AMIDE, CARBAMATE, AND UREA DERIVATIVES

The present invention relates to the potentiation of glutamate receptor function using certain amide, carbamate and urea derivatives. It also relates to novel amide, carbamate and urea derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

In the mammalian central nervous system (CNS), the transmission of nerve impulses is controlled by the interaction between a neurotransmitter, that is released by a sending neuron, and a surface receptor on a receiving neuron, which causes excitation of this receiving neuron. L-Glutamate, which is the most abundant neurotransmitter in the CNS, mediates the major excitatory pathway in mammals, and is referred to as an excitatory amino acid (EAA). The receptors that respond to glutamate are called excitatory amino acid receptors (EAA receptors). See Watkins & Evans, *Ann. Rev. Pharmacol. Toxicol.*, 21, 165 (1981); Monaghan, Bridges, and Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); Watkins, Krogsgaard-Larsen, and Honore, *Trans. Pharm. Sci.*, 11, 25 (1990). The excitatory amino acids are of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic". This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists *N*-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid (KA). The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in c-AMP formation, and changes in ion channel function. Schoepp

and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). Both types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways, but also participate in the modification of synaptic connections during development and throughout life. Schoepp, Bockaert, and Sladeczek, *Trends in Pharmacol. Sci.*, 11, 508 (1990); McDonald and Johnson, *Brain Research Reviews*, 15, 41 (1990).

AMPA receptors are assembled from four protein sub-units known as GluR1 to GluR4, while kainic acid receptors are assembled from the sub-units GluR5 to GluR7, and KA-1 and KA-2. Wong and Mayer, *Molecular Pharmacology* 44: 505-510, 1993. It is not yet known how these sub-units are combined in the natural state. However, the structures of certain human variants of each sub-unit have been elucidated, and cell lines expressing individual sub-unit variants have been cloned and incorporated into test systems designed to identify compounds which bind to or interact with them, and hence which may modulate their function. Thus, European patent application, publication number EP-A2-0574257 discloses the human sub-unit variants GluR1B, GluR2B, GluR3A and GluR3B. European patent application, publication number EP-A1-0583917 discloses the human sub-unit variant GluR4B.

One distinctive property of AMPA and kainic acid receptors is their rapid deactivation and desensitization to glutamate. Yamada and Tang, *The Journal of Neuroscience*, September 1993, 13(9): 3904-3915 and Kathryn M. Partin, *J. Neuroscience*, November 1, 1996, 16(21): 6634-6647. The physiological implications of rapid desensitization, and deactivation if any, are unknown.

It is known that the rapid desensitization and deactivation of AMPA and/or kainic acid receptors to glutamate may be inhibited using certain compounds. This action of these compounds is often referred to in the alternative as "potentiation" of the receptors. One such compound, which selectively potentiates AMPA receptor function, is cyclothiazide. Partin et al., *Neuron*. Vol. 11, 1069-1082, 1993. Compounds which potentiate AMPA receptors, like cyclothiazide, are often referred to as ampakines.

International Patent Application Publication Number WO 9625926 discloses a group of phenylthioalkylsulphonamides, S-oxides and homologs

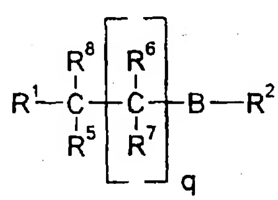
which are said to potentiate membrane currents induced by kainic acid and AMPA.

Ampakines have been shown to improve memory in a variety of animal tests. Staubli *et al.*, *Proc. Natl. Acad. Sci.*, Vol. 91, pp 777-781, 1994, *Neurobiology*, and Arai *et al.*, *The Journal of Pharmacology and Experimental Therapeutics*, 278: 627-638, 1996.

It has now been found that cyclothiazide and certain amide, carbamate and urea derivatives potentiate agonist-induced excitability of human GluR4B receptor expressed in HEK 293 cells. Since cyclothiazide is known to potentiate glutamate receptor function *in vivo*, it is believed that this finding portends that the amide, carbamate and urea derivatives will also potentiate glutamate receptor function *in vivo*, and hence that the compounds will exhibit ampakine-like behavior.

In addition, certain sulfonamide derivatives which potentiate glutamate receptor function in a mammal have been disclosed in International Patent Application Publication WO 98/33496 published August 6, 1998.

The present invention provides compounds of formula I:



formula I

wherein

B is $CONR^a$, NR^aCO, NR^aCO_2 or NR^aCONR^a;

R^a represents hydrogen or (1-6C) alkyl,

q is zero or 1;

R^1 represents a naphthyl group or a phenyl, furyl, thienyl or pyridyl group which is unsubstituted or substituted by one or two substituents selected independently from halogen; nitro; cyano; hydroxyimino; (1-10C)alkyl; (2-10C)alkenyl; (2-10C)alkynyl; (3-8C)cycloalkyl; hydroxy(3-8C)cycloalkyl; oxo(3-8C)cycloalkyl;

halo(1-10C)alkyl; $(CH_2)_yX^1R^9$ in which y is 0 or an integer of from 1 to 4, X^1 represents O, S, NR^{10}, CO, COO, OCO, $CONR^{11}$, $NR^{12}CO$, $NR^{12}COCOO$ or $OCONR^{13}$, R^9 represents hydrogen, (1-10C)alkyl, (3-10C)alkenyl, (3-10C)alkynyl, pyrrolidinyl, tetrahydrofuryl, morpholino or (3-8C)cycloalkyl and R^{10}, R^{11}, R^{12} and R^{13} each independently represents hydrogen or (1-10C)alkyl, or R^9 and R^{10}, R^{11}, R^{12} or R^{13} together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperidinyl or morpholino group; N-(1-4C)alkylpiperazinyl; N-phenyl(1-4C)alkylpiperazinyl; thienyl; furyl; oxazolyl; isoxazolyl; pyrazolyl; imidazolyl; thiazolyl; pyridyl; pyridazinyl; pyrimidinyl; dihydro-thienyl; dihydrofuryl; dihydrothiopyranyl; dihydropyranyl; dihydrothiazolyl; (1-4C)alkoxycarbonyldihydrothiazolyl; (1-4C)alkoxycarbonyldimethyldihydrothiazolyl; tetrahydro-thienyl; tetrahydrofuryl; tetrahydrothiopyranyl; tetrahydropyranyl; indolyl; benzofuryl; benzothienyl; benzimidazolyl; and a group of formula R^{14}-$(L^a)_n$-X^2-$(L^b)_m$ in which X^2 represents a bond, O, NH, S, SO, SO_2, CO, CH(OH), CONH, NHCO, NHCONH, NHCOO, COCONH, OCH_2CONH or CH=CH, L^a and L^b each represent (1-4C)alkylene, one of n and m is 0 or 1 and the other is 0, and R^{14} represents a phenyl or heteroaromatic group which is unsubstituted or substituted by one or two of halogen, nitro, cyano, hydroxyimino, (1-10C) alkyl, (2-10C)alkenyl, (2-10C)alkynyl, (3-8C)-cycloalkyl, 4-(1,1-dioxotetrahydro-1,2-thiazinyl), halo(1-10C)alkyl, cyano(2-10C)alkenyl, phenyl, and $(CH_2)_zX^3R^{15}$ in which z is 0 or an integer of from 1 to 4, X^3 represents O, S, NR^{16}, CO, CH(OH), COO, OCO, $CONR^{17}$, $NR^{18}CO$, $NHSO_2$, $NHSO_2NR^{17}$, NHCONH, $OCONR^{19}$ or $NR^{19}COO$, R^{15} represents hydrogen, (1-10C)alkyl, phenyl(1-4C)alkyl, halo(1-10C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkylsulfonylamino(1-4C)alkyl, (N-(1-4C)alkoxycarbonyl)(1-4C)alkylsulfonylamino-(1-4C)alkyl, (3-10C)alkenyl, (3-10C)alkynyl, (3-8C)-cycloalkyl, camphoryl or an aromatic or heteroaromatic group which is unsubstituted or substituted by one or two of halogen, (1-4C)alkyl, halo(1-4C)alkyl, di(1-4C)alkylamino and (1-4C)alkoxy and R^{16}, R^{17}, R^{18} and

R^{19} each independently represents hydrogen or (1-10C)alkyl, or R^{15} and R^{16}, R^{17}, R^{18} or R^{19} together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperidinyl or morpholino group;

R^2 represents hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, chloro(1-6C)alkyl, (2-6C)alkenyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylCO_2(1-4C)alkyl, phenyl(1-6C)alkyl, heteroaromatic, phenyl which is unsubstituted or substituted by halogen, (1-4C)alkyl or (1-4C)alkoxy, or a group of formula R^3R^4N in which R^3 and R^4 each independently represents (1-4C)alkyl or, together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperidinyl, morpholino, piperazinyl, hexahydroazepinyl or octahydroazocinyl group; and

R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, (1-6C)alkyl; aryl(1-6C)alkyl; (2-6C)alkenyl; aryl(2-6C)alkenyl and aryl; or

two of R^5, R^6, R^7 and R^8 together with the carbon atom or carbon atoms to which they are attached form a (3-8C) carbocyclic ring; and the remainder of R^5, R^6, R^7 and R^8 represent hydrogen; or a pharmaceutically acceptable salt thereof;

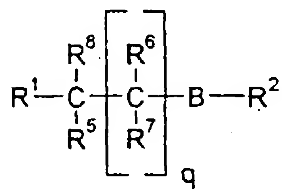
with the proviso that when R^2 represents R^3R^4N, then B is other than NR^aCONR^a or $CONR^a$.

The present invention further provides a method of potentiating glutamate receptor function in a mammal requiring such treatment, which comprises administering an effective amount of a compound of formula I.

According to another aspect, the present invention provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof as defined hereinabove for the manufacture of a medicament for potentiating glutamate receptor function.

In addition, the present invention provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof for potentiating glutamate receptor function.

The invention further provides a method of potentiating glutamate receptor function in a mammal requiring such treatment, which comprises administering an effective amount of a compound of formula:



wherein

B is $CONR^a$, NR^aCO, NR^aCO_2 or NR^aCONR^a;

R^a represents hydrogen or (1-6C) alkyl,

q is zero or 1;

R^1 represents an unsubstituted or substituted aromatic or heteroaromatic group;

R^2 represents hydrogen, (1-6C)alkyl, (3-6C)cycloalkyl, fluoro(1-6C)alkyl, chloro(1-6C)alkyl, (2-6C)alkenyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylCO_2(1-4C)alkyl, phenyl(1-6C)alkyl, heteroaromatic, phenyl which is unsubstituted or substituted by halogen, (1-4C)alkyl or (1-4C)alkoxy, or a group of formula R^3R^4N in which R^3 and R^4 each independently represents (1-4C)alkyl or, together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperidinyl, morpholino, piperazinyl, hexahydroazepinyl or octahydroazocinyl group; and

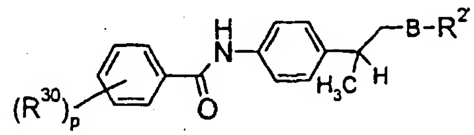
R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, (1-6C)alkyl; aryl(1-6C)alkyl; (2-6C)alkenyl; aryl(2-6C)alkenyl and aryl; or

two of R^5, R^6, R^7 and R^8 together with the carbon atom or carbon atoms to which they are attached form a (3-8C) carbocyclic ring; and the remainder of R^5,

R^6, R^7 and R^8 represent hydrogen; or a pharmaceutically acceptable salt thereof;

with the proviso that when R^2 represents R^3R^4N, then B is other than NR^aCONR^a or $CONR^a$.

It is further understood that the following compounds of formula I' are further included within the scope of the present invention:



formula I'

wherein

B represents $CONR^a$, NR^aCO, NR^aCO_2 or NR^aCONR^a;

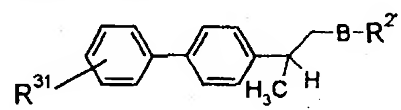
R^a represents hydrogen or (1-6C) alkyl;

$R^{2'}$ represents (1-4C)alkyl;

R^{30} represents hydrogen, F, Cl, Br, I, CN, CF_3, NH_2, NO_2, CH_3CONH, (1-4C)alkyl, (1-4C)alkoxy, and phenyl; and

P is 0, 1, 2 or 3; or a pharmaceutically acceptable salt thereof.

In addition, the following compounds of formula I" are further included within the scope of the present invention:



formula I"

wherein

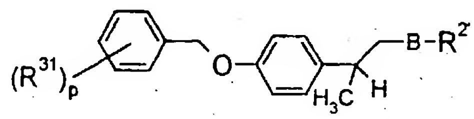
B represents $CONR^a$, NR^aCO, NR^aCO_2 or NR^aCONR^a;

R^a represents hydrogen or (1-6C) alkyl;

$R^{2'}$ represents (1-4C)alkyl; and

R^{31} represents hydrogen, F, Cl, Br, I, CN, CF_3, NH_2, (1-4C)alkyl, (1-4C)alkoxy, $-CH_2NHSO_2R^{2''}$, $-(CH_2CH_2)NHSO_2R^{2''}$, and $-(CH_2CH_2CH_2)NHSO_2R^{2''}$ wherein $R^{2''}$ represents (1-4C)alkyl; or a pharmaceutically acceptable salt thereof.

In addition, the following compounds of formula I''' are further included within the scope of the present invention:



formula I'''

wherein

B represents $CONR^a$, NR^aCO, NR^aCO_2 or NR^aCONR^a;

R^a represents hydrogen or (1-6C) alkyl;

$R^{2'}$ represents (1-4C)alkyl; and

R^{31} represents hydrogen, F, Cl, Br, I, CN, CF_3, NH_2, (1-4C)alkyl, (1-4C)alkoxy, $-CH_2NHSO_2R^{2''}$, $-(CH_2CH_2)NHSO_2R^{2''}$, and $-(CH_2CH_2CH_2)NHSO_2R^{2''}$ wherein $R^{2''}$ represents (1-4C)alkyl;

P is 0, 1, 2 or 3; or a pharmaceutically acceptable salt thereof.

A preferred value for B is NR^aCO with NHCO being especially preferred.

A preferred value for R^a is hydrogen.

Preferred values for $R^{2'}$ are methyl, ethyl and isopropyl, with isopropyl being most preferred.

Preferred values for $R^{2''}$ are methyl, ethyl and isopropyl, with methyl being most preferred.

Preferred values for R^{30} are hydrogen, methyl, ethyl, isopropyl, Fl, Cl, CF_3, CH_3CONH and CN.

Preferred values for R^{31} are hydrogen, Fl, Cl, CN, methyl, ethyl, isopropyl, CF_3, and $-(CH_2CH_2)NHSO_2R^{2''}$, with $-(CH_2CH_2)NHSO_2CH_3$ being especially preferred.

Preferred values for p are 0, 1 or 2.

In this specification, the term "potentiating glutamate receptor function" refers to any increased responsiveness of glutamate receptors, for example AMPA receptors, to glutamate or an agonist, and includes but is not limited to

inhibition of rapid desensitization or deactivation of AMPA receptors to glutamate.

A wide variety of conditions may be treated or prevented by the compounds of formula I and their pharmaceutically acceptable salts through their action as potentiators of glutamate receptor function. Such conditions include those associated with glutamate hypofunction, such as psychiatric and neurological disorders, for example cognitive disorders; neuro-degenerative disorders such as Alzheimer's disease; age-related dementias; age-induced memory impairment; movement disorders such as tardive dyskinesia, Hungtington's chorea, myoclonus and Parkinson's disease; reversal of drug-induced states (such as cocaine, amphetamines, alcohol-induced states); depression; attention deficit disorder; attention deficit hyperactivity disorder; psychosis; cognitive deficits associated with psychosis; and drug-induced psychosis. The compounds of formula I may be further useful for the treatment of sexual dysfunction. The compounds of formula I may also be useful for improving memory (both short term and long term) and learning ability. The present invention provides the use of compounds of formula I for the treatment of each of these conditions.

The term “treating” (or “treat”) as used herein includes its generally accepted meaning which encompasses prohibiting, preventing, restraining, and slowing, stopping, or reversing progression, severity, or a resultant symptom.

The present invention includes the pharmaceutically acceptable salts of the compounds defined by formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, g-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. It is further understood that the above salts may form hydrates or exist in a substantially anhydrous form.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the enantiomers of compounds of formula I can be resolved by one of ordinary skill in the art using standard techniques well known in the art,

such as those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981. Examples of resolutions include recrystallization techniques or chiral chromatography.

Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

As used herein, the term "aromatic group" means the same as aryl, and includes phenyl and a polycyclic aromatic carbocyclic ring such as naphthyl.

The term "heteroaromatic group" includes an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, and a bicyclic group consisting of a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or another 5-6 membered ring containing one to four atoms selected from oxygen, sulfur and nitrogen. Examples of heteroaromatic groups are thienyl, furyl, oxazolyl, isoxazolyl, oxadiazoyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl,

pyrimidyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl and quinolyl.

The term "substituted" as used in the term "substituted aromatic or heteroaromatic group" herein signifies that one or more (for example one or two) substituents may be present, said substituents being selected from atoms and groups which, when present in the compound of formula I, do not prevent the compound of formula I from functioning as a potentiator of glutamate receptor function.

Examples of substituents which may be present in a substituted aromatic or heteroaromatic group include halogen; nitro; cyano; hydroxyimino; (1-10C) alkyl; (2-10C)alkenyl; (2-10C)alkynyl; (3-8C)cycloalkyl; hydroxy(3-8C)cycloalkyl; oxo(3-8C)cycloalkyl; halo(1-10C)alkyl; $(CH_2)_yX^1R^9$ in which y is 0 or an integer of from 1 to 4, X^1 represents O, S, NR^{10}, CO, COO, OCO, $CONR^{11}$, $NR^{12}CO$, $NR^{12}COCOO$, $OCONR^{13}$, R^9 represents hydrogen, (1-10C) alkyl, (3-10C)alkenyl, (3-10C)alkynyl, pyrrolidinyl, tetrahydrofuryl, morpholino or (3-8C)cycloalkyl and R^{10}, R^{11}, R^{12} and R^{13} each independently represents hydrogen or (1-10C)alkyl, or R^9 and R^{10}, R^{11}, R^{12} or R^{13} together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperidinyl or morpholino group; N-(1-4C)alkylpiperazinyl; N-phenyl(1-4C)alkylpiperazinyl; thienyl; furyl; oxazolyl; isoxazolyl; pyrazolyl; imidazolyl; thiazolyl; pyridyl; pyridazinyl; pyrimidinyl; dihydrothienyl; dihydrofuryl; dihydrothiopyranyl; dihydropyranyl; dihydrothiazolyl; (1-4C)alkoxycarbonyl dihydrothiazolyl; (1-4C)alkoxycarbonyl dimethyl-dihydrothiazolyl; tetrahydrothienyl; tetrahydrofuryl; tetrahydrothiopyranyl; tetrahydropyranyl; indolyl; benzofuryl; benzothienyl; benzimidazolyl; and a group of formula R^{14}-$(L^a)_n$-X^2-$(L^b)_m$ in which X^2 represents a bond, O, NH, S, SO, SO_2, CO, CH(OH), CONH, NHCO, NHCONH, NHCOO, COCONH, OCH_2CONH, or CH=CH, L^a and L^b each represent (1-4C)alkylene, one of n and m is 0 or 1 and the other is 0, and R^{14} represents a phenyl or heteroaromatic group which is unsubstituted or substituted by one or two of halogen; nitro; cyano; (1-10C) alkyl;

(2-10C)alkenyl; (2-10C)alkynyl; (3-8C)cycloalkyl; 4-(1,1-dioxotetrahydro-1,2-thiazinyl); halo(1-10C)alkyl; cyano(2-10C)alkenyl; phenyl; and $(CH_2)_zX^3R^{15}$ in which z is 0 or an integer of from 1 to 4, X^3 represents O, S, NR^{16}, CO, CH(OH), COO, OCO, $CONR^{17}$, $NR^{18}CO$, $NHSO_2$, $NHSO_2NR^{17}$, $OCONR^{19}$ or $NR^{19}COO$, R^{15} represents hydrogen, (1-10C)alkyl, phenyl(1-4C)alkyl, halo(1-10C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkylsulfonylamino(1-4C)alkyl, N-(1-4C)alkoxycarbonyl)(1-4C)alkylsulfonylamino(1-4C)alkyl, (3-10C)alkenyl, (3-10C)alkynyl, (3-8C)cycloalkyl, camphoryl, or an aromatic or heteroaromatic group which is unsubstituted or substituted by one or two of halogen, (1-4C)alkyl, halo(1-4C)alkyl, di(1-4C)alkylamino and (1-4C)alkoxy, and R^{16}, R^{17}, R^{18} and R^{19} each independently represents hydrogen or (1-10C)alkyl, or R^{15} and R^{16}, R^{17}, R^{18} or R^{19} together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperidinyl or morpholino group.

The term (1-10C)alkyl includes (1-8C)alkyl, (1-6C)alkyl and (1-4C)alkyl. Particular values are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl.

The term (2-10C)alkenyl includes (3-10C)alkenyl, (1-8C)alkenyl, (1-6C)alkenyl and (1-4C)alkenyl. Particular values are vinyl and prop-2-enyl.

The term (2-10C)alkynyl includes (3-10C)alkynyl, (1-8C)alkynyl, (1-6C)alkynyl and (3-4C)alkynyl. A particular value is prop-2-ynyl.

The term (1-4C)alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, and the like.

The term (3-8C)cycloalkyl, as such or in the term (3-8C)cycloalkyloxy, includes monocyclic and polycyclic groups. Particular values are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and bicyclo[2.2.2]octane. The term includes (3-6C)cycloalkyl: cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term hydroxy(3-8C)cycloalkyl includes hydroxy-cyclopentyl, such as 3-hydroxycyclopentyl.

The term oxo(3-8C)cycloalkyl includes oxocyclopentyl, such as 3-oxocyclopentyl.

The term halogen includes fluorine, chlorine, bromine and iodine.

The term halo(1-10C)alkyl includes fluoro(1-10C)alkyl, such as trifluoromethyl and 2,2,2-trifluoroethyl, and chloro(1-10C)alkyl such as chloromethyl.

The term phenyl(1-6C)alkyl includes the term $-CH_2$phenyl.

The term cyano(2-10C)alkenyl includes 2-cyanoethenyl.

The term (2-4C)alkylene includes ethylene, propylene and butylene. A preferred value is ethylene.

The term thienyl includes thien-2-yl and thien-3-yl.

The term furyl includes fur-2-yl and fur-3-yl.

The term oxazolyl includes oxazol-2-yl, oxazol-4-yl and oxazol-5-yl.

The term isoxazolyl includes isoxazol-3-yl, isoxazol-4-yl and isoxazol-5-yl.

The term oxadiazolyl includes [1,2,4]oxadiazol-3-yl and [1,2,4]oxadiazol-5-yl.

The term pyrazolyl includes pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl.

The term thiazolyl includes thiazol-2-yl, thiazol-4-yl and thiazol-5-yl.

The term thiadiazolyl includes [1,2,4]thiadiazol-3-yl, and [1,2,4]thiadiazol-5-yl.

The term isothiazolyl includes isothiazol-3-yl, isothiazol-4-yl and isothiazol-5-yl.

The term imidazolyl includes imidazol-2-yl, imidazolyl-4-yl and imidazolyl-5-yl.

The term triazolyl includes [1,2,4]triazol-3-yl and [1,2,4]triazol-5-yl.

The term tetrazolyl includes tetrazol-5-yl.

The term pyridyl includes pyrid-2-yl, pyrid-3-yl and pyrid-4-yl.

The term pyridazinyl includes pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl and pyridazin-6-yl.

The term pyrimidyl includes pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl and pyrimidin-6-yl.

The term benzofuryl includes benzofur-2-yl and benzofur-3-yl.

The term benzothienyl includes benzothien-2-yl and benzothien-3-yl.

The term benzimidazolyl includes benzimidazol-2-yl.

The term benzoxazolyl includes benzoxazol-2-yl.

The term benzothiazolyl includes benzothiazol-2-yl.

The term indolyl includes indol-2-yl and indol-3-yl.

The term quinolyl includes quinol-2-yl.

The term dihydrothiazolyl includes 4,5-dihydrothiazol-2-yl, and the term (1-4C)alkoxycarbonyldihydrothiazolyl includes 4-methoxycarbonyl-4,5-dihydrothiazol-2-yl.

Preferably either one or two of R^5, R^6, R^7 and R^8 represents (1-6C)alkyl, aryl(1-6C)alkyl, (2-6C)alkenyl, aryl(2-6C)alkenyl or aryl, or two of R^5, R^6, R^7 and R^8 together with the carbon atom or carbon atoms to which they are attached form a (3-8C)carbocyclic ring; and the remainder of R^5, R^6, R^7 and R^8 represent hydrogen.

Examples of a (1-6C)alkyl group represented by R^5, R^6, R^7 and R^8 are methyl, ethyl and propyl. An example of an aryl(1-C)alkyl group is benzyl. An example of a (2-6C)alkenyl group is prop-2-enyl. An example of a (3-8C)carbocyclic ring is a cyclopropyl ring.

More preferably R^6 and R^7 represent hydrogen.

Preferably R^5 and R^8 each independently represents hydrogen or (1-4C)alkyl, or together with the carbon atom to which they are attached form a (3-8C) carbocyclic ring.

More preferably R^8 represents methyl or ethyl, or R^5 and R^8 together with the carbon atom to which they are attached form a cyclopropyl ring. When R^8 represents methyl or ethyl, R^5 preferably represents hydrogen or methyl.

Especially preferred are compounds in which R^8 represents methyl and R^5, R^6 and R^7 represent hydrogen.

Preferably R^3 and R^4 each represent methyl.

Examples of values for R^2 are methyl, ethyl, propyl, 2-propyl, butyl, 2-methylpropyl, cyclohexyl, trifluoromethyl, 2,2,2-trifluoroethyl, chloromethyl, ethenyl, prop-2-enyl, methoxyethyl, phenyl, 4-fluorophenyl, or dimethylamino. Preferably R^2 is ethyl, 2-propyl or dimethylamino.

Examples of values for R^9 are hydrogen, methyl, ethyl, propyl, isopropyl, t-butyl, ethenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-pyrrolidinyl, morpholino or 2-tetrahydrofuryl.

Examples of values for R^{15} are hydrogen, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, benzyl, 2,2,2-trifluoroethyl, 2-methoxycarbonylethyl, cyclohexyl, 10-camphoryl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 1-(5-dimethylamino)naphthyl, and 2-thienyl.

X^1 preferably represents O, CO, CONH or NHCO.

z is preferably 0.

R^9 is preferably (1-4C)alkyl, (2-4C)alkenyl, (3-6C)cycloalkyl, pyrrolidinyl, morpholino or tetrahydrofuryl.

Particular values for the groups $(CH_2)_yX^1R^9$ and $(CH_2)_zX^3R^{15}$ include (1-10C)alkoxy, including (1-6C)alkoxy and (1-4C)alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy and isobutoxy; (3-10C)alkenyloxy, including (3-6C)alkenyloxy, such as prop-2-enyloxy; (3-10C)alkynyloxy, including (3-6C)alkynyloxy, such as prop-2-ynyloxy; and (1-6C)alkanoyl, such as formyl and ethanoyl.

Examples of particular values for y are 0 and 1.

Examples of particular values for z are 0, 1, 2 and 3.

L^a and L^b preferably each independently represents CH_2.

X^2 preferably represents a bond, O, NH, CO, CH(OH), CONH, NHCONH or OCH_2CONH.

Preferably the group $(CH_2)yX^1R^9$ represents CHO; $COCH_3$, OCH_3; $OCH(CH_3)_2$; $NHCOR^9$ in which R^9 represents methyl, ethyl, isopropyl, t-butyl, ethenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-pyrolidinyl or morpholino; $CONHR^9$ in which R^9 represents cyclopropyl or cyclopentyl; $NHCOCOOCH_3$; or 2-tetrahydrofurylmethoxy.

Preferably the group $(CH_2)_zX^3R^{15}$ represents NH_2; CH_2NH_2; $(CH_2)_2NH_2$; $(CH_2)_3NH_2$; $CONH_2$; $CONHCH_3$; $CON(CH_3)_2$; $N(C_2H_5)_2$; CH_2OH;

$CH(OH)CH_3$; $CH(OH)CH_2CH_2$; CHO; $COCH_3$; COOH; $COOCH_3$; $CH_2NHCOOC(CH_3)_3$; $(CH_2)_2NHCOOC(CH_3)_3$; $NHSO_2CH(CH_3)_2$; a group of formula $(CH_2)_2NHSO_2R^{15}$ in which R^{15} represents CH_3, CH_2CH_3, $CH(CH_3)_2$, $(CH_2)_2CH_3$, $(CH_3)_3CH_3$, benzyl, CH_2CF_3, 2-methoxycarbonylethyl, cyclohexyl, 10-camphoryl, phenyl, 2-fluorophenyl, 4-fluorophenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-methoxyphenyl, 1-(2-dimethylamino)naphthyl or 2-thienyl; $CH(OH)CH_2NHSO_2CH_3$; $(CH_2)_3NHSO_2CH(CH_3)_2$; $COCH_2N(OCOC(CH_3)_2SO_2CH_3$; $COCH_2NHSO_2CH_3$; $(CH_2)_2NHCOR^{15}$ in which R^{15} represents CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, phenyl, 3-fluorophenyl, 4-fluorophenyl, benzyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-thienyl, CH=CH, CH=CHCN, OCH_3 or $O(CH_2)_3CH_3$.

Examples of particular values for $(L^a)_n$-X^2-$(L^b)_m$ are a bond, O, NH, S, SO, SO_2, CO, CH_2, $COCH_2$, COCONH, $CH(OH)CH_2$, CONH, NHCO, NHCONH, CH_2O, OCH_2, OCH_2CONH, CH_2NH, $NHCH_2$ and CH_2CH_2.

R^{14} is preferably an unsubstituted or substituted phenyl, naphthyl, furyl, thienyl, isoxazolyl, thiazolyl, tetrazolyl, pyridyl, pyrimidyl benzothienyl or benzothiazolyl group.

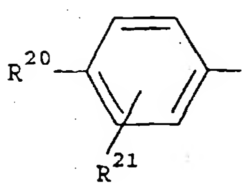
Examples of particular values for R^{14} are phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chloro-phenyl, 3-chlorophenyl, 4-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 4-iodophenyl, 2,3-difluoro-phenyl, 2,4-difluorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 4-cyanophenyl, 3-nitrophenyl, 4-hydroxyiminophenyl, 2-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 3-propylphenyl, 4-t-butylphenyl, 2-prop-2-enylphenyl, 4-(4-(1,1-dioxotetrahydro-1,2-thiazinyl)phenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-bromomethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-(2-cyanoethenyl)phenyl, 4-phenyl, 2-formylphenyl, 3-formylphenyl, 4-formylphenyl, 2-acetylphenyl, 3-acetylphenyl, 4-acetylphenyl, 2-propanoylphenyl, 2-(2-methyl-propanoyl)phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-butoxyphenyl, 2-hydroxymethylphenyl, 4-hydroxymethylphenyl, 2-(1-hydroxyethyl)phenyl, 3-(1-hydroxyethyl)phenyl, 4-(1-

hydroxyethyl)phenyl, 2-(1-hydroxypropyl)phenyl, 4-(1-hydroxypropyl)phenyl, 2-(1-hydroxy-2,2-dimethyl-propyl)phenyl, 4-trifluoromethoxyphenyl, 2-aminophenyl,4-aminophenyl, 4-N,N-diethylaminophenyl, 4-aminomethylphenyl, 4-(2-aminoethyl)phenyl, 4-(3-aminopropyl)phenyl, 4-carboxyphenyl, 4-carbamoylphenyl, 4-N-methylcarbamoylphenyl, 4-N,N-dimethylcarbamoylphenyl, 2-isopropylaminomethylphenyl, 4-t-butoxycarbonylaminomethylphenyl, 4-(2-isopropoxy-carboxamido)ethylphenyl, 4-(2-t-butoxycarboxamido)ethyl-phenyl, 4-isopropylsulfonylaminophenyl, 4-(2-methane-sulfonylamino)ethylphenyl, 4-(2-ethylsulfonylamino)ethyl-phenyl, 4-(3-isopropylsulfonylamino)propylphenyl, 4-(1-(2-(2-propane)sulfonylamino)propyl)phenyl, 4-(2-propylsulfonyl-amino)ethylphenyl, 4-(2-isopropylsulfonylamino)ethylphenyl, 4-(2-butylsulfonylamino)ethylphenyl, 4-(1-isopropyl-sulfonylaminomethyl)ethylphenyl, 4-(1-hydroxy-2-methane-sulfonylamino)ethylphenyl, 4-(2-(2,2,2-trifluoroethyl)-sulfonylaminoethyl)phenyl, 4-(2-cyclohexylsulfonylamino)-ethylphenyl, 4-(2-(2,2,2-trifluoroethyl)sulfonylamino)-ethylphenyl, 4-(2-N,N-dimethylaminosulfonylamino)-ethylphenyl, 4-(2-phenylsulfonylaminoethyl)phenyl, 4-(2-(2-fluorophenyl)sulfonylaminoethyl)phenyl, 4-(2-(4-fluoro-phenyl)sulfonylaminoethyl)phenyl, 4-(2-(2-trifluoromethyl-phenyl)sulfonylaminoethyl)phenyl, 4-(2-(4-trifluoro-methylphenyl)sulfonylaminoethyl)phenyl, 4-(2-(4-methoxyphenyl)sulfonylaminoethyl)phenyl, 4-(2-(1-(5-dimethylamino)napthalenesulfonylamino)ethyl)phenyl, 4-(2-(2-thienyl)sulfonylamino)ethyl)phenyl, 4-(2-benzamidoethyl)-phenyl, 4-(2-(4-fluorobenzamido)ethyl)phenyl, 4-(2-(3-methoxybenzamido)ethyl)phenyl, 4-(2-(3-fluorobenzamido)-ethyl)phenyl, 4-(2-(4-methoxybenzamido)ethyl)phenyl, 4-(2-(2-methoxybenzamido)ethyl)phenyl, 4-(1-(2-(2-methoxy-carbonylethanesulfonylamino)ethyl)phenyl, 4-(1-(2-(10-camphorsulfonylamino)ethyl)phenyl, 4-(1-(2-(benzylsulfonyl-amino)ethyl)phenyl, 4-(2-phenylacetamido)ethyl)phenyl, 4-methanesulfonylaminoethanoylphenyl, 4-(N-(t-butoxy-carbonyl)methanesulfonylaminoethanoyl)phenyl, 4-(2-(2-thienylcarboxamido)ethyl)phenyl, thien-2-yl, 5-hydroxy-methylthien-2-yl, 5-formylthien-2-yl, thien-3-yl, 5-hydroxymethylthien-3-yl, 5-formylthien-3-yl, 2-

bromothien-3-yl, fur-2-yl, 5-nitrofur-2-yl, fur-3-yl, isoxazol-5-yl, 3-bromoisoxazol-5-yl, isoxazol-3-yl, 5-trimethylsilylisoxazol-3-yl, 5-methylisoxazol-3-yl, 5-hydroxymethylisoxazol-3-yl, 5-methyl-3-phenylisoxazol-4-yl, 5-(2-hydroxyethyl)isoxazol-3-yl, 5-acetylisoxazol-3-yl, 5-carboxyisoxazol-3-yl, 5-N-methylcarbamoylisoxazol-3-yl, 5-methoxycarbonylisoxazol-3-yl, 3-bromo[1,2,4]oxadiazol-5-yl, pyrazol-1-yl, thiazol-2-yl, 4-hydroxymethylthiazol-2-yl, 4-methoxycarbonylthiazol-2-yl, 4-carboxythiazol-2-yl, imidazol-1-yl, 2-sulfhydryl-imidazol-1-yl, [1,2,4]triazol-1-yl, tetrazol-5-yl, 2-methyltetrazol-5-yl, 2-ethyltetrazol-5-yl, 2-isopropyl-tetrazol-5-yl, 2-(2-propenyl)tetrazol-5-yl, 2-benzyl-tetrazol-5-yl, pyrid-2-yl, 5-ethoxycarbonylpyrid-2-yl, pyrid-3-yl, 6-chloropyrid-3-yl, pyrid-4-yl, 5-trifluoro-methylpyrid-2-yl, 6-chloropyridazin-3-yl, 6-methylpyridazin-3-yl, 6-methoxypyrazin-3-yl, pyrimidin-5-yl, benzothien-2-yl, benzothiazol-2-yl, and quinol-2-yl.

Examples of an unsubstituted or substituted aromatic or heteroaromatic group represented by R^1 are unsubstituted or substituted phenyl, furyl, thienyl (such as 3-thienyl) and pyridyl (such as 3-pyridyl) .

More preferably, R^1 represents 2-naphthyl or a group of formula



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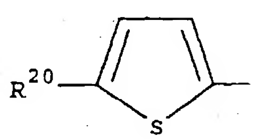

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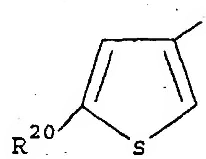

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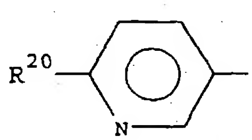


in which

R^{20} represents halogen; nitro; cyano; hydroxyimino; (1-10C)alkyl; (2-10C)alkenyl; (2-10C)alkynyl; (3-8C)cyclo-alkyl; hydroxy(3-8C)cycloalkyl; oxo(3-8C)cycloalkyl; halo(1-10C)alkyl; $(CH_2)_yX^1R^9$ in which y is 0 or an integer of from

1 to 4, X^1 represents O, S, NR^{10}, CO, COO, OCO, $CONR^{11}$, $NR^{12}CO$, $NR^{12}COCOO$, $OCONR^{13}$, R^9 represents hydrogen, (1-10C) alkyl, (3-10C)alkenyl, (3-10C)alkynyl, pyrrolidinyl, tetrahydrofuryl, morpholino or (3-8C)cycloalkyl and R^{10}, R^{11}, R^{12} and R^{13} each independently represents hydrogen or (1-10C)alkyl, or R^9 and R^{10}, R^{11}, R^{12} or R^{13} together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperidinyl or morpholino group; N-(1-4C)alkylpiperazinyl; N-phenyl(1-4C)alkylpiperazinyl; thienyl; furyl; oxazolyl; isoxazolyl; pyrazolyl; imidazolyl; thiazolyl; tetrazolyl; pyridyl; pyridazinyl; pyrimidinyl; dihydrothienyl; dihydrofuryl; dihydrothiopyranyl; dihydropyranyl; dihydrothiazolyl; (1-4C)alkoxycarbonyl-dihydrothiazolyl; (1-4C)alkoxycarbonyldimethyl-dihydrothiazolyl; tetrahydrothienyl; tetrahydrofuryl; tetrahydrothiopyranyl; tetrahydropyranyl; indolyl; benzofuryl; benzothienyl; benzimidazolyl; benzothiazolyl; and a group of formula R^{14}-$(L^a)_n$-X^2-$(L^b)_m$ in which X^2 represents a bond, O, NH, S, SO, SO_2, CO, CH(OH), CONH, NHCONH, NHCOO, COCONH, OCH_2CONH or CH=CH, NHCO, L^a and L^b each represent (1-4C)alkylene, one of n and m is 0 or 1 and the other is 0, and R^{14} represents a phenyl or hetero-aromatic group which is unsubstituted or substituted by one or two of halogen; nitro; cyano; (1-10C)alkyl; (2-10C)alkenyl; (2-10C)alkynyl; (3-8C)cycloalkyl; 4-(1,1-dioxotetrahydro-1,2-thiazinyl); halo(1-10C)alkyl; cyano(2-10C)alkenyl; phenyl; $(CH_2)_zX^3R^{15}$ in which z is 0 or an integer of from 1 to 4, X^3 represents O, S, NR^{16}, CO, CH(OH), COO, OCO, $CONR^{17}$, $NR^{18}CO$, $NHSO_2$, $NHSO_2NR^{17}$, NHCONH, $OCONR^{19}$ or $NR^{19}COO$, R^{15} represents hydrogen, (1-10C)alkyl, phenyl(1-4C)alkyl, halo(1-10C)alkyl, (1-4C)alkoxycarbonyl(1-4C)alkyl, (1-4C)alkylsulfonylamino(1-4C)alkyl, (N-(1-4C)alkoxycarbonyl)(1-4C)alkylsulfonylamino(1-4C)alkyl, (3-10C)alkenyl, (3-10C)alkynyl, (3-8C)cycloalkyl, camphoryl or an aromatic or heteroaromatic group which is unsubstituted or substituted by one or two of halogen, (1-4C)alkyl, halo(1-4C)alkyl, di(1-4C)alkylamino and (1-4C)alkoxy, and R^{16}, R^{17}, R^{18} and R^{19} each independently represents hydrogen or (1-10C)alkyl, or R^{15} and R^{16},

R^{17}, R^{18} or R^{19} together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperidinyl or morpholino group; and

R^{21} represents a hydrogen atom, a halogen atom, a (1-4C)alkyl group or a (1-4C)alkoxy group.

Examples of particular values for R^{20} are fluorine, chlorine, bromine, cyano, hydroxyimino, methyl, ethyl, propyl, 2-propyl, butyl, 2-methylpropyl, 1,1-dimethylethyl, cyclopentyl, cyclohexyl, 3-hydroxycyclopentyl, 3-oxocyclopentyl, methoxy, ethoxy, propoxy, 2-propoxy, acetyl, acetylamino, ethylcarboxamido, propylcarboxamido, 1-butanoylamido, t-butylcarboxamido, acryloylamido, 2-pyrrolidinylcarboxamido, 2-tetrahydrofurylmethoxy, morpholinocarboxamido, methyloxalylamido, cyclo-propylcarboxamido, cyclobutylcarboxamido, cyclopentyl-carboxamido, cyclohexylcarboxamido, cyclopropylcarbamoyl, cyclopentylcarbamoyl, pyrrolidin-1-yl, morpholino, piperidin-1-yl, N-methylpiperazinyl, N-benzylpiperazinyl, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, isoxazol-3-yl, thiazol-2-yl, tetrazol-5-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrimidin-5-yl, 4,5-dihydrothiazol-2-yl, 4,5-dihydro-4-methoxycarbonylthiazol-2-yl, 4,5-dihydro-4-methoxy-carbonyl-5,5-dimethylthiazol-2-yl, benzothien-2-yl, benzothiazol-2-yl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 2,3-difluorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3-nitrophenyl, 4-cyanophenyl, 2-methylphenyl, 4-methylphenyl, 4-(4-(1,1-dioxotetrahydro-1,2-thiazinyl)phenyl, 3-trifluoromethylphenyl, 4-trifluoro-methylphenyl, 4-(2-cyanoethenyl)phenyl, 2-formylphenyl, 3-formylphenyl, 4-formylphenyl, 3-acetyl-phenyl, 4-acetylphenyl, 4-carboxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-hydroxymethylphenyl, 4-hydroxymethylphenyl, 3-(1-hydroxyethyl)phenyl, 4-(1-hydroxyethyl)phenyl, 4-(1-hydroxypropyl)phenyl, 2-aminophenyl, 4-aminophenyl, 4-N,N-diethylaminophenyl, 4-aminomethylphenyl, 4-(2-aminoethyl)-phenyl, 4-(3-aminopropyl)phenyl, 4-(2-acetylaminoethyl)-phenyl, 4-t-butoxycarboxylaminoethyl)phenyl, 4-(2-t-butoxycarboxylaminoethyl)phenyl, benzylsulfonylamino, 4-isopropylsulfonylaminophenyl, 4-(2-methanesulfonyl-aminoethyl)phenyl, 4-(2-ethylsulfonylaminoethyl)phenyl, 4-(2-propylsulfonylaminoethyl)phenyl, 4-(2-butylsulfonyl-aminoethyl)phenyl, 4-(2-

isopropylsulfonylaminoethyl)phenyl, 4-(1-hydroxy-2-methanesulfonylaminoethyl)phenyl, 4-(2-dimethylaminosulfonylaminoethyl)phenyl, 4-(1-(2-(2-propyl)sulfonylaminopropyl)phenyl, 4-(2-(2,2,2-trifluoro-ethyl)sulfonylaminoethyl)phenyl, 4-(2-cyclohexylsulfonyl-aminoethyl)phenyl, 4-(2-phenylsulfonylaminoethyl)phenyl, 4-(2-(2-fluorophenyl)sulfonylaminoethyl)phenyl, 4-(2-(4-fluorophenyl)sulfonylaminoethyl)phenyl, 4-(2-(2-trifluoromethylphenyl)sulfonylaminoethyl)phenyl, 4-(2-(4-trifluoromethylphenyl)sulfonylaminoethyl)phenyl, 4-(2-(4-methoxyphenyl)sulfonylaminoethyl)phenyl, 4-(2-(1-(5-dimethylamino)napthalenesulfonylamino)ethyl)phenyl, 4-(2-(2-thienyl)sulfonylamino)ethyl)phenyl, 4-(2-benzamidoethyl)-phenyl, 4-(2-(4-fluorobenzamido)ethyl)phenyl, 4-(2-(3-methoxybenzamido)ethyl)phenyl, 4-(2-(3-fluorobenzamido)-ethyl)phenyl, 4-(2-(4-methoxybenzamido)ethyl)phenyl, 4-(2-(2-methoxybenzamido)ethyl)phenyl, 4-(2-(2-thienyl-carboxamido)ethyl)phenyl, 4-carbamoylphenyl, 4-methyl-carbamoylphenyl, 4-dimethylcarbamoylphenyl, 4-(2-(2-methylpropaneamido)ethyl)phenyl, 4-(2-(3-methyl-butaneamido)ethyl)phenyl, benzoylmethyl, benzamido, 2-fluorobenzamido, 3-flurobenzamido, 4-fluorobenzamido, 2,4-difluorobenzamido, 3-chlorobenzamido, 4-chlorobenzamido, 4-bromobenzamido, 4-iodobenzamido, 4-cyanobenzamido, 3-methylbenzamido, 4-methylbenzamido, 4-ethylbenzamido, 4-propylbenzamido, 4-t-butylbenzamido, 4-vinylbenzamido, 2-trifluoromethylbenzamido, 3-trifluoromethylbenzamido, 4-trifluoromethylbenzamido, 2-fluoro-4-trifluoromethyl-benzamido, 2-methoxybenzamido, 3-methoxybenzamido, 4-methoxybenzamido, 4-butoxybenzamido, 4-phenylphenyl-carboxamido, 4-benzylcarboxamido, 4-phenoxymethyl-carboxamido, 2-fluorobenzylamino, benzyloxy, 2-fluoro-benzyloxy, 2-hydroxy-2-phenylethyl, 2-fluorophenylcarbamoyl, 4-(1-(2-(2-methoxycarbonylethanesulfonylamino)ethyl)phenyl, 4-(1-(2-(10-camphorsulfonylamino)ethyl)phenyl, 4-(1-(2-(benzylsulfonylamino)ethyl)phenyl, 4-(2-phenylacetamido)-ethyl)phenyl, 4-(methanesulfonylaminoethanoyl)phenyl, 4-(N-t-butoxycarbonyl)methanesulfonylaminoethanoyl)phenyl, 2-

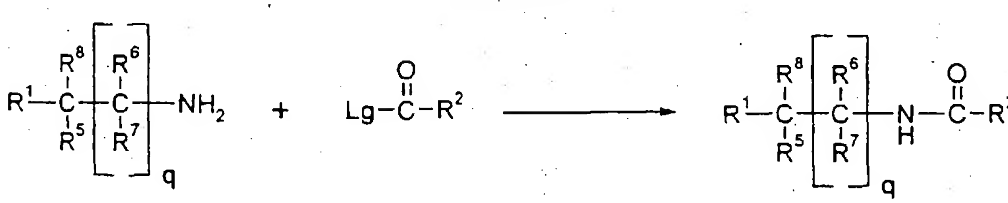
thienylcarboxamido, 2-furylcarboxamido, 3-(5-methyl-isoxazolyl)carboxamido, 5-isoxazolylcarboxamido, 2-benzothienylcarboxamido, 4-(5-methyl-3-phenylisoxazolyl)-carboxamido, 4-pyridylcarboxamido, 2-(5-nitrofuryl)-carboxamido, 2-pyridylcarboxamido, 6-chloro-2-pyridyl-carboxamido, 2-thienylsulfonamido, 2-thienylmethylamino, 3-thienylmethylamino, 2-furylmethylamino, 3-furylmethylamino, 3-acetylureido and 2-(2-thienyl)ethylureido.

Examples of particular values for R^{21} are hydrogen and chlorine. R^{21} is preferably ortho to R^{20}.

Examples of particular values for R^1 are 2-naphthyl, 4-bromophenyl, 4-cyanophenyl, 4-benzamidophenyl, 4-methylphenyl, 4-isopropyl-phenyl, 4-isobutylphenyl, 4-*t*-butylphenyl, 4-methoxyphenyl, 4-isopropoxyphenyl, 4-cyclopentylphenyl, 4-cyclohexylphenyl, 4-(2-hydroxymethylphenyl)phenyl, 4-(4-hydroxymethylphenyl)-phenyl, 4-(2-furyl)phenyl, 4-(3-furyl)phenyl, 4-(2-thienyl)-phenyl, 4-(3-thienyl)phenyl, 4-(pyrrolidin-1-yl)phenyl, 4-(piperidin-l-yl)phenyl, 3-chloro-4-piperidin-1-ylphenyl, 4-benzyloxyphenyl, 4-(2-fluorophenyl)phenyl, 4-(3-fluoro-phenyl)phenyl, 4-(2-formylphenyl)phenyl, 4-(3-formylphenyl)-phenyl, 4-(4-formylphenyl)phenyl, 4-(4-methylphenyl)phenyl and 4-(2-methoxyphenyl)phenyl.

The compounds of formula I can be prepared as described in Schemes 1-V below. The reagents and starting materials are readily available to one of ordinary skill in the art. All the substituents, unless otherwise specified are previously defined.

Scheme I



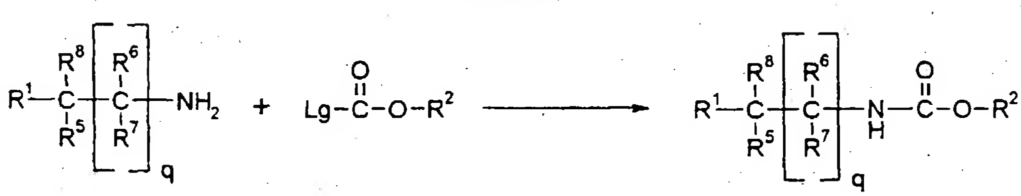
formula II formula IIIa formula Ia

In Scheme I, the compounds of formula Ia are prepared from compounds of formula II and formula IIIa under standard amide forming conditions well

known to one of ordinary skill in the art. For examples of standard amide forming conditions see J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," 2nd Edition, McGraw Hill Inc., (1977) pages 382-386, and T.W Green, "Protective Groups in Organic Synthesis," John Wiley & Sons, Inc. (1981) pages 249-266.

More specifically, for example, an amine of formula II is dissolved in a suitable organic solvent, such as tetrahydrofuran or methylene chloride and treated with an equivalent of a compound of formula IIIa wherein "Lg" represents a suitable leaving group. Examples of suitable leaving groups are Cl, Br, I, (1-6C)alkyl(C=O)O-, and the like. The reaction can be performed at a temperature of from about -5°C to about 50°C, preferably at a temperature of about 0°C to about 25°C. After about 2 hours to about 12hours, the product, formula Ia, is isolated and purified by techniques well known in the art, such as extraction techniques and chromatography. For example, the reaction is diluted with a suitable organic solvent, such as methylene chloride, rinsed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The crude product can then be purified by flash chromatography on silica gel with a suitable eluent, such ethyl acetate/hexanes to provide the purified compound of formula Ia.

Scheme II



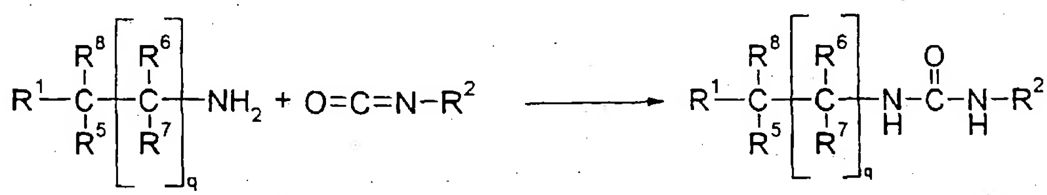
formula II formula IIIb formula Ib

In Scheme II, the compounds of formula Ib are prepared from compounds of formula II and formula IIIb under standard carbamate forming conditions well known to one of ordinary skill in the art. For examples of standard carbamate forming conditions see J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," 2nd Edition, McGraw Hill Inc., (1977) pages 382-

383, and T.W Green, "Protective Groups in Organic Synthesis," John Wiley & Sons, Inc. (1981) pages 223-248.

More specifically, for example, an amine of formula II is dissolved in a suitable organic solvent, such as tetrahydrofuran or methylene chloride and treated with an equivalent of a compound of formula IIIb wherein "Lg" represents a suitable leaving group. Examples of suitable leaving groups are Cl, Br, I, and the like. The reaction can be performed at a temperature of from about -10°C to about 50°C, preferably at a temperature of about 0°C to about 25°C. After about 2 hours to about 12 hours, the product, formula Ib, is isolated and purified by techniques well known in the art, such as extraction techniques and chromatography. For example, the reaction is diluted with a suitable organic solvent, such as methylene chloride, rinsed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The crude product can then be purified by flash chromatography on silica gel with a suitable eluent, such ethyl acetate/hexanes to provide the purified compound of formula Ib.

<u>Scheme III</u>

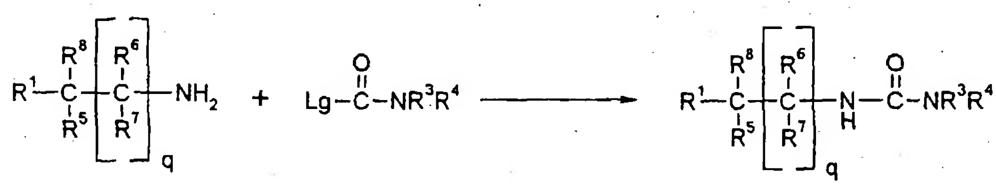


formula II formula IIIc formula Ic

In Scheme III, the compounds of formula Ic are prepared from compounds of formula II and formula IIIc under standard urea forming conditions well known to one of ordinary skill in the art. For examples of standard urea forming conditions see J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," 2nd Edition, McGraw Hill Inc., (1977) page 823, and T.W Green, "Protective Groups in Organic Synthesis," John Wiley & Sons, Inc. (1981) pages 248-49.

More specifically, for example, a compound of formula II is dissolved in a suitable organic solvent, such as methylene chloride, and the solution is treated with about 1.1 equivalents of an isocyanate of formula IIIc. The reaction can be performed at a temperature of about -10°C to about 50°C for about 2 hours to about 12 hours to provide the urea of formula Ic. The urea of formula Ic can be isolated and purified by techniques well known in the art, such as extraction techniques and chromatography. For example, the reaction is diluted with a suitable organic solvent, such as methylene chloride, rinsed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product can then be purified by flash chromatography on silica gel with a suitable eluent, such ethyl acetate/hexanes to provide the purified urea of formula Ic.

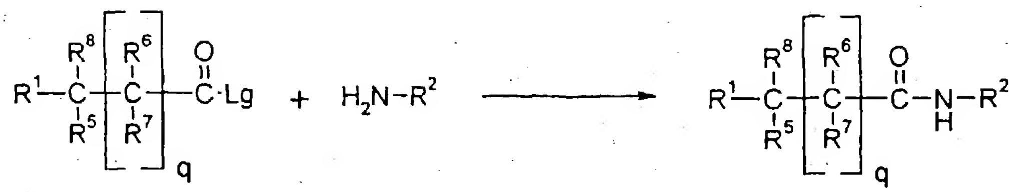
Scheme IV



formula II formula IIId formula Id

Ureas of formula Id can be prepared from a compound of formula II and the compound of formula IIId under standard conditions well known in the art. "Lg" represents a suitable leaving group. Examples of suitable leaving groups are Cl, Br, I, and the like. Examples of a compound of formula IIId are N,N-dimethylcarbamoyl chloride, N,N-diethylcarbamoyl chloride, pyrrolidine carbonyl chloride, 4-morpholine carbonyl chloride, and the like. The reaction is performed under standard amide forming conditions in a manner analogous to the procedure described previously in Scheme I.

Scheme V



formula IV formula V formula Ie

In Scheme V, the compound of formula Ie is prepared from the compound of formula IV and formula V under standard amide forming conditions in a manner analogous to the conditions described previously in Scheme I.

The compounds of formula I in which R^1 represents a 4-bromophenyl group may conveniently be converted into other compounds of formula I in which R represents another 4-substituted phenyl group by reaction with an appropriate boronic acid derivative, for example, a benzeneboronic acid derivative. The reaction is conveniently performed in the presence of a tetrakis (triarylphosphine)palladium(0) catalyst, such as tetrakis (triphenylphosphine)palladium(0) and a base such as potassium carbonate. Convenient solvents for the reaction include aromatic hydrocarbons, such as toluene. The temperature at which the reaction is conducted is conveniently in the range of from 0 to 150°C, preferably 75 to 120°C. Bis aromatic intermediates useful in the preparation of compounds of formula I may be prepared by reacting a bromoaromatic or bromoheteroaromatic compound with an aromatic or heteroaromatic boronic acid in an analogous manner.

More specifically, for example, to a degassed solution of a compound of formula I wherein R^1 represents a 4-bromophenyl group, approximately 1.5 equivalents of a benzeneboronic acid derivative, such as 3-fluorobenzeneboronic acid, and approximately 1.5 equivalents of potassium carbonate in a suitable organic solvent, such as toluene, is added a catalytic amount of bis(triphenyl-phosphine)palladium(II) dichloride. The mixture is heated to about 100°C for about 16 hours, cooled to ambient temperature and diluted with ethyl acetate. The mixture is washed with water and the organic portion is separated. The aqueous portion is extracted with ethyl acetate and the

combined organics are dried anhydrous magnesium sulfate, filtered and concentrated under vacuum. Chromatography on silica gel with a suitable eluent, such as ethyl acetate/toluene provides the desired bis aromatic compound of formula I.

The boronic acid derivative used as a starting material may be prepared by reacting a trialkyl borate, such as triisopropyl borate with an appropriate organolithium compound at reduced temperature. For example, 2-fluoro-benzeneboronic acid may be prepared by reacting 2-fluorobromobenzene with butyllithium in tetrahydrofuran at about -78°C to afford 2-fluorophenyl lithium, and then reacting this organolithium compound with triisopropyl borate.

Alternatively, the compounds of formula I in which R^1 represents a 4-bromophenyl group may be converted to a 4-(trimethylstannyl)phenyl or 4-(tri-n-butylstannyl)phenyl group by treatment of the corresponding bromide with a palladium(0) catalyst, such as tetrakis(triphenylphosphine)-palladium(0) and hexaalkyldistannane, where the alkyl group is methyl or *n*-butyl, in an aprotic solvent such as toluene in the presence of a tertiary amine base such as triethyl-amine, at temperatures ranging from 80 to 140°C, preferably from 90 to 110°C.

The compounds of formula I in which R^1 represents a 4-(tri-*n*-butylstannyl)phenyl group may then be reacted with an aryl- or heteroarylbromide, such as 2-bromothiophene-5-carboxaldehyde, in the presence of a palladium(0) catalyst, such as tetrakis(triphenylphosphine)palladium(0), or a palladium(II) catalyst, such as bis(triphenylphosphine)-palladium(II) dichloride, in an aprotic solvent, such as dioxane, at temperatures ranging from 80 to 140°C, preferably from 90 to 110°C, to afford the corresponding 4-(aryl)phenyl or 4-(heteroaryl)phenyl substituted compound.

The compounds of formula I in which R^1 represents a 4-bromophenyl group may be converted into other compounds of formula I in which R^1 represents a 4-substituted alkyl- or cycloalkylphenyl group, such as 4-cyclopentylphenyl by treatment of the corresponding bromide with an appropriate alkyl- or cycloalkyl Grignard reagent, such as cyclopentyl-magnesium bromide,

in the presence of a palladium(II) catalyst, such as [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II)($PdCl_2$(dppf)), in an aprotic solvent, such as diethyl ether at temperatures ranging from -78°C to 25°C.

The compounds of formula I in which R^1 represents a 4-bromophenyl group may be converted into a 4-substituted carboxyaldehydephenyl(formylphenyl) group by reaction of the corresponding bromide with the carbon monoxide gas which is bubbled into the reaction under atmospheric pressure in the presence of a palladium(II) catalyst, such as bis(triphenyl-phosphine)palladium(II) dichloride and sodium formate in an aprotic solvent, such as dimethylformamide at temperatures ranging from 70 to 110°C, preferably at 90°C.

The compounds of formula I in which R^1 represents a 4-hydroxyphenyl group may be converted into other compounds of formula I in which R^1 represents an alkoxy group by treatment of the corresponding hydroxyphenyl group with an appropriate alkylhalide such as benzylbromide in the presence of sodium hydride in an aprotic solvent such as dimethylformamide at temperatures ranging from 25 to 100°C, preferably from 50 to 90°C.

The ability of compounds of formula I to potentiate glutamate receptor-mediated response may be determined using fluorescent calcium indicator dyes (Molecular Probes, Eugene, Oregon, Fluo-3) and by measuring glutamate-evoked efflux of calcium into GluR4 transfected HEK293 cells, as described in more detail below.

In one test, 96 well plates containing confluent monolayers of HEK cells stably expressing human GluR4B (obtained as described in European Patent Application Publication Number EP-A1-583917) are prepared. The tissue culture medium in the wells is then discarded, and the wells are each washed once with 200 µl of buffer (glucose, 10mM, sodium chloride, 138mM, magnesium chloride, 1mM, potassium chloride, 5mM, calcium chloride, 5mM, N-[2-hydroxyethyl]-piperazine-N-[2-ethanesulfonic acid], 10mM, to pH 7.1 to 7.3). The plates are then incubated for 60 minutes in the dark with 20 µM Fluo3-AM

dye (obtained from Molecular Probes Inc., Eugene, Oregon) in buffer in each well. After the incubation, each well is washed once with 100 µl buffer, 200 µl of buffer is added and the plates are incubated for 30 minutes.

Solutions for use in the test are also prepared as follows. 30 µM, 10 µM, 3 µM and 1 µM dilutions of test compound are prepared using buffer from a 10 mM solution of test compound in DMSO. 100 µM cyclothiazide solution is prepared by adding 3 µl of 100 mM cyclothiazide to 3 ml of buffer. Control buffer solution is prepared by adding 1.5 µl DMSO to 498.5 µl of buffer.

Each test is then performed as follows. 200 µl of control buffer in each well is discarded and replaced with 45 µl of control buffer solution. A baseline fluorescent measurement is taken using a FLUOROSKAN II fluorimeter (Obtained from Labsystems, Needham Heights, MA, USA, a Division of Life Sciences International Plc). The buffer is then removed and replaced with 45 µl of buffer and 45 µl of test compound in buffer in appropriate wells. A second fluorescent reading is taken after 5 minutes incubation. 15 µl of 400 µM glutamate solution is then added to each well (final glutamate concentration 100 µM), and a third reading is taken. The activities of test compounds and cyclothiazide solutions are determined by subtracting the second from the third reading (fluorescence due to addition of glutamate in the presence or absence of test compound or cyclothiazide) and are expressed relative to enhance fluorescence produced by 100 µM cyclothiazide.

In another test, HEK293 cells stably expressing human GluR4 (obtained as described in European Patent Application Publication No. EP-A1-0583917) are used in the electro-physiological characterization of AMPA receptor potentiators. The extracellular recording solution contains (in mM): 140 NaCl, 5 KCl, 10 HEPES, 1 $MgCl_2$, 2 $CaCl_2$, 10 glucose, pH = 7.4 with NaOH, 295 mOsm kg-1. The intracellular recording solution contains (in mM): 140 CsCl, 1 $MgCl_2$, 10 HEPES, (N-[2-hydroxyethyl]piperazine-N1-[2-ethanesulfonic acid]) 10 EGTA (ethylene-bis(oxyethylene-nitrilo)tetraacetic acid), pH = 7.2 with CsOH, 295 mOsm kg-1. With these solutions, recording pipettes have a resistance of 2-3 MΩ. Using the whole-cell voltage clamp technique (Hamill et al.(1981)Pflügers Arch., 391: 85-100), cells are voltage-clamped at -60mV and control current

responses to 1 mM glutamate are evoked. Responses to 1 mM glutamate are then determined in the presence of test compound. Compounds are deemed active in this test if, at a test concentration of 10 μM, they produce a greater than 30% increase in the value of the current evoked by 1 mM glutamate.

In order to determine the potency of test compounds, the concentration of the test compound, both in the bathing solution and co-applied with glutamate, is increased in half log units until the maximum effect was seen. Data collected in this manner are fit to the Hill equation, yielding an EC_{50} value, indicative of the potency of the test compound. Reversibility of test compound activity is determined by assessing control glutamate 1mM responses. Once the control responses to the glutamate challenge are re-established, the potentiation of these responses by 100 μM cyclothiazide is determined by its inclusion in both the bathing solution and the glutamate-containing solution. In this manner, the efficacy of the test compound relative to that of cyclothiazide can be determined.

According to another aspect, the present invention provides a pharmaceutical composition, which comprises a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinabove and a pharmaceutically acceptable diluent or carrier.

The pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragcanth, gelatin, calcium silicate, micro-crystalline

cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. Compositions of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 mg to about 500 mg, more preferably about 5 mg to about 300 mg (for example 25 mg) of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantify (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium Stearate	10
Total	**460**

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 60 mg of active ingredient are made as follows:

	Quantity (mg/tablet)
Active Ingredient	60
Starch	45
Microcrystalline Cellulose	35
Polyvinylpyrrolidone	4
Sodium Carboxymethyl Starch	4.5
Magnesium Stearate	0.5
Talc	1
Total	**150**

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

As used herein the term "patient" refers to a mammal, such a mouse, guinea pig, rat, dog or human. It is understood that the preferred patient is a human.

As used herein the term "effective amount" refers to the amount or dose of the compound which provides the desired effect in the patient under diagnosis or treatment.

The particular dose of compound administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal,

subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg.

The following examples represent typical syntheses of compounds within formula I as described generally above. These examples are illustrative only and are not intended to limit the invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art. As used herein, the following terms have the meanings indicated: "eq" refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "L" refers to liters; "mL" refers to milliliters; "μL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "min" refers to minutes; "h" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ"refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to methyl sulfoxide; "LDA" refers to lithium diisopropylamide; "aq" refers to aqueous; "TFA" refers to trifluoroacetic acid: "iPrOAc" refers to isopropyl acetate; "EtOAc" refers to ethyl acetate; "Me" refers to a methyl group: "Et" refers to an ethyl group: "iPr" refers to an isopropyl group; "Bu" refers to a butyl group; and "RT" refers to room temperature.

Preparation 1

2-(4-Bromophenyl)propionitrile

A solution of 50.0 g (225.0 mmol) of 4-bromophenyl-acetonitrile and 1.8 g (12.8 mmol) of potassium carbonate in 387 mL of dimethyl carbonate was heated to 180°C in a sealed vessel for 16 hours. The solution was then cooled, diluted with 200 mL of ethyl acetate and washed once with 100 mL water, once with 100 mL of 10% aqueous sodium bisulfate and once with 100 mL brine. The organic portion was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was

distilled under vacuum through a short path distillation apparatus to afford 40.3 g (85%) of the title compound.

Preparation 2

2-(4-Bromophenyl)propylamine hydrochloride

To a solution of 35.2 g (167.6 mmol) of material from Preparation 1 under reflux in 35.0 mL of tetrahydrofuran was added 18.4 mL (184.3 mmol) of 10M borane-dimethyl-sulfide slowly via a syringe. The solution was heated under reflux for an additional 1 hour after the addition was complete. The solution was cooled to ambient temperature and a saturated solution of hydrogen chloride in methanol was added slowly until pH 2 was achieved. The resulting slurry was concentrated *in vacuo*. The residue was dissolved in methanol and concentrated *in vacuo* twice. The resulting solid was suspended in ethyl ether, filtered, rinsed with ethyl ether and dried *in vacuo* to afford 31.2 g (74%) of the title compound.

Preparation 3

2-Fluorobenzeneboronic Acid

A solution of 50 g (285.6 mmol) of 2-fluorobromobenzene in 400 mL of tetrahydrofuran was cooled to -78°C and 200 mL (320.0 mmol) of 1.6M n-Butyllithium was added via a cannula. The mixture was stirred at -78°C for 60 minutes, then 98.9 mL (428.4 mmol) of triisopropyl borate was added via a cannula and stirring was continued for 60 minutes. The cooling bath was removed and the mixture was stirred at ambient temperature for 1.5 hours, then 150 mL of 6N hydrochloric acid was added and stirring was continued for 1.5 hours. To the mixture was added 100 mL of brine, and then the organic layer was separated and the aqueous layer was extracted three times with 30 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*.. The residue was recrystallized from water to afford 25.2 g (63%) of the title compound.

Preparation 4

2-(4-bromophenyl)-N-(*t*-butoxycarbonyl)propylamine

To a solution of 11.8 g (55.0 mmol) of material from Preparation 2 in 100 mL of chloroform and 100 mL of saturated sodium bicarbonate was added 12.0 g (55.0 mmol) of di-*tert*-butyl dicarbonate. The solution was stirred at ambient temperature for 1 hour. The organic layer was separated and the aqueous layer was extracted three times with 30 mL each of chloroform. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 16.5 g (95%) of the title compound.

Preparation 5

2-(4-(2-fluorophenyl)phenyl)-N-(*t*-butoxycarbonyl)propylamine

To a degassed solution of 12.5 g (39.8 mmol) of material from Preparation 4, 6.7 g (47.7 mmol) of material from Preparation 3 and 8.2 g (59.7 mmol) of potassium carbonate in 140 mL of toluene was added 2.3 g (1.9 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90°C for 18 hours. The mixture was then cooled to ambient temperature and 300 mL of water and 150 mL of ether were added. The organic layer was separated and the aqueous layer was extracted three times with 50 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (500 g of silica gel, 10% ethyl acetate/hexanes) of the residue afforded 9.3 g (71%) of the title compound.

Preparation 6

2-(4-(2-fluorophenyl)phenyl)propylamine

A solution of 9.3 g of material from Preparation 5 in 100 mL 20% trifluoroacetic acid/dichloromethane was stirred at ambient temperature for 2 hours. The mixture was concentrated *in vacuo* to afford 11.7 g of material. The material was dissolved in 100 mL of ether and washed twice with 50 mL of 1N sodium hydroxide. The organic layer was concentrated *in vacuo* to afford 5.48 g (85%) of the title compound.

Preparation 7

2-(4-Isopropylphenyl)propionitrile

In a 250 mL flask, 4-isopropylphenylacetonitrile 8.00 g (50.2 mmol) was dissolved in tetrahydrofuran (150 mL) under a nitrogen atmosphere. The solution was cooled to -78°C and lithium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 52.8 mL (52.8 mmol) added. The resulting mixture was stirred at -78°C for 1 hour. To this reaction mixture was added iodomethane 3.29 mL (52.8 mmol). The resulting mixture was slowly allowed to warm to ambient temperature over 16 hours then quenched with 0.2M hydrochloric acid and extracted twice with diethyl ether. The organic fractions were combined, dried ($MgSO_4$) and concentrated under vacuo. Chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 6.32 g (73%) of the title compound.

Field Desorption Mass Spectrum: M = 173.

Analysis for $C_{12}H_{15}N$:

Theory: C, 83.19; H, 8.73; N, 8.08.

Found: C, 82.93; H, 8.57, N, 8.02.

Preparation 8

2-(4-Isopropylphenyl)propylamine hydrochloride

In a 100 mL flask, fitted with a condenser, 2-(4-isopropylphenyl) propionitrile 1.90 g (11.0 mmol) was dissolved in tetrahydrofuran (70 mL) under a nitrogen atmosphere. Borane-methyl sulfide complex (10.0-10.2 M in tetrahydrofuran, 1.20 mL, 12.1 mmol) was added to the solution and the mixture heated to reflux for 3 hours. The solution was cooled to ambient temperature and a saturated solution of hydrochloric acid in methanol added slowly until a white precipitate formed. The solvent was removed *in vacuo* and the resulting white solid triturated (x4) with diethyl ether. Drying under vacuo gave 1.76 g (73%) of the title compound.

Preparation 9

2-(4-Methoxyphenyl)propionitrile

Following the method of Preparation 7, but using 4-methoxyphenylacetonitrile 5.00 g (34.0 mmol), 6.32 g of the title compound was obtained.

Field Desorption Mass Spectrum: M = 161.

Analysis for $C_{10}H_{11}NO$:

Theory: C, 74.51; H, 6.88; N, 8.69.

Found: C, 74.34; H, 6.67; N, 8.93.

Preparation 10

2-(4-Methoxyphenyl)propylamine hydrochloride

Following the method of Preparation 8, but using the product of Preparation 9, 2.75 g (17.1 mmol), 2.77 g (81%) of the title compound was obtained.

Analysis for $C_{10}H_{16}ClNO$:

Theory: C, 59.55; H, 8.00; N, 6.94.

Found: C, 59.33; H, 7.89; N, 6.71.

Preparation 11

Methyl 2-(4-*t*-butylphenyl)propanoate

23.3 mL of lithium bis (trimethylsilyl) amide (1.0 M, 23 mmols) was added dropwise to 4.75 g (23 mmol) of methyl 4-tert-butylphenylacetate in 100 mL of dry THF at -78°C while stirring under nitrogen. The mixture was stirred at this temperature for 45 minutes, then 1.5 mL (24 mmol) methyl iodide was added dropwise and the solution was stirred for an additional 1 hour at -78°C. The mixture was poured into 200 mL of H_2O and the desired product was extracted with 500 mL diethyl ether. The organic layer was backwashed once with 500 mL H_2O, dried over K_2CO_3, and concentrated under reduced pressure to yield 5.12 g of a dark oil. The oil was purified via silica gel chromatography eluting with a solvent gradient of hexanes to hexanes/ethyl acetate 19:1. The fractions

containing the desired product were combined and concentrated under reduced pressure to yield the title compound 2.65 g (53%).

Mass Spectrum: M = 220.

Preparation 12

Methyl 2-(4-*t*-butylphenyl)butanoate

4 g (19 mmol) of methyl 4-tert-butylphenylacetate, 19.5 mL (1.0 M, 19 mmol) of lithium bis (trimethylsilyl) amide and 3.12 g (20 mmol) of ethyl iodide were reacted as described in Preparation 11 to yield 5.13 g of a brown oil. Chromatography, eluting with a gradient solvent of hexanes to hexanes/ethyl acetate 19:1 gave the title compound 2.35 g (53%).

Mass Spectrum: M = 234.

Preparation 13

Methyl 2-(4-*t*-butylphenyl)-2-methylpropanoate

4.75 g (23 mmol) of methyl 4-tert-butylphenylacetate, 46.6 mL (1.0 M, 46 mmol) of lithium bis (trimethylsilyl) amide, and 6.80 g (48 mmols) of methyl iodide were reacted as described in Preparation 11 to yield 4.73 g of a crude oil. Chromatography, eluting with a solvent gradient of hexanes to hexanes/ethyl acetate 19:1, gave the title compound 2.0 g (37%).

Mass Spectrum: M = 234.

Preparation 14

Ethyl 2-(2-naphthyl)propanoate

5 g (23 mmol) of ethyl 2-naphthylacetate, 23.3 mL (1.0 M, 23 mmol) of lithium bis (trimethylsilyl) amide, and 1.5 mL (24 mmol) of methyl iodide were reacted as described in Preparation 11 to yield 5.71 g of a dark oil. Chromatography eluting with a solvent gradient of hexanes to hexanes/ethyl acetate 19:1 gave the title compound 2.85 g (54%).

Mass Spectrum: M = 228.

Preparation 15

2-(4-*t*-butylphenyl)propanoic Acid

2.60 g (12 mmol) of the product of Preparation 11 and 1.75 g (42 mMol) of lithium hydroxide were placed into a tri-solvent solution of tetrahydrofuran (189 mL), CH_3OH (63 mL), and H_2O (63 mL) and stirred at ambient temperature for 16 hours. The mixture was then concentrated under reduced pressure and the resulting white solid was taken into 200 mL 1N HCl and the desired product was extracted with 250 mL ethyl acetate. The organic layer was concentrated under reduced pressure to give the title compound 1.21 g (49%).

Mass Spectrum: M = 206.

Preparation 16

2-(4-*t*-butylphenyl)butanoic Acid

The title compound (2.14 g) was prepared by the method of Preparation 15, starting from the product of Preparation 12, and recrystallized from hexanes.

Mass Spectrum: M = 220.

Preparation 17

2-(4-*t*-butylphenyl)-2-methylpropanoic Acid

The title compound (1.75 g) was prepared by the method of Preparation 15 starting from the product of Preparation 13, and recrystallized from hexanes.

Mass Spectrum: M = 220.

Preparation 18

2-(2-Naphthyl)propanoic Acid

The title compound (3.81 g) was prepared by the method of Preparation 15 starting from the product of Preparation 14, and recrystallized from hexanes/ethyl acetate 9:1.

Mass Spectrum: M = 214.

Preparation 19

2-(4-*t*-butylphenyl)propionamide

900 mg (4.4 mmol) of the product of Preparation 15 was added portionwise to oxalyl chloride (10 mL) at ambient temperature under N_2 followed by CH_2Cl_2 (10 mL). Initiation of the reaction was accomplished by the addition of one drop of DMF. An evolution of gas appeared and the reaction was stirred at ambient temperature for 2 hours. The solution was concentrated under reduced pressure to yield an oil. Dioxane (10 mL) was added for solubility and while stirring at ambient temperature, 28% ammonium hydroxide (10 mL) was added and the reaction was stirred for 16 hours. The solution was then concentrated under reduced pressure to yield a white solid. This solid was taken into 50 mL ethyl acetate, backwashed once with 50 mL H_2O, dried over K_2CO_3, and concentrated under reduced pressure to yield 770 mg of a solid. Recrystallization from hexanes/ethyl acetate 1:1 gave the title compound 555 mg (61%).

Mass Spectrum: M = 205.

Preparation 20

2-(4-*t*-butylphenyl)butanamide

The title compound was prepared by the method of Preparation 19, starting from the product of Preparation 16. Purification was achieved by silica gel chromatography (Chromatotron-2000 micron rotor) eluting with a solvent of hexanes/ethyl acetate 1:1 to yield 471 mg (60%).

Mass Spectrum: M = 219.

Preparation 21

2-(4-*t*-butylphenyl)-2-methylpropionamide

The title compound was prepared following the method of Preparation 19, starting from the product of Preparation 17. The crude product was triturated with a solution of hexanes/-ethyl acetate 19:1 for 1/2 hour and filtered to yield

1.16 g of a white solid. Subsequent recrystallization from ethyl acetate/ethanol 1:1 gave an 80% recovery as platelets.

Mass Spectrum: M = 219.

Preparation 22

2-(2-Naphthyl)propionamide

The title compound was prepared following the method of Preparation 19, starting from the product of Preparation 18. Recrystallization from hexanes/ethyl acetate 1:1 yielded 1.65 g (90%).

Mass Spectrum: M = 199.

Preparation 23

2-(4-*t*-butylphenyl)propylamine

25 mL of Borane-tetrahydrofuran complex (1.0 M, .025 Mol) was added via a syringe to 1.10 g (5.4 mmol) of the product of Preparation 19 (60 mL) at ambient temperature under N_2. The mixture was then heated at 60°-65°C for 16 hours. A saturated HCl/methanol solution (5 mL) was then added via a syringe at ambient temperature with severe foaming and the solution was then concentrated under reduced pressure. The resulting white solid was taken into 100 mL 1 N NaOH and the liberated free amine was extracted once with 200 ml diethyl ether. The organic layer was backwashed once with 200 mL H_2O, dried over K_2CO_3, and concentrated under reduced pressure to yield 1.21 g of a brown oil. Chromatography (Chromatotron-2000 micron rotor) eluting with a gradient solvent of ethyl acetate/MeOH 9:1 to MeOH gave 856 mg (83%).

Mass Spectrum: M = 191.

Preparation 24

2-(4-*t*-butylphenyl)butylamine

The title compound 540 mg was prepared as an oil by the method of Preparation 23, starting from the product of Preparation 20.

Mass Spectrum: M = 205.

Preparation 25

2-(4-*t*-butylphenyl)-2-methylpropylamine

The title compound 428 mg (42%) was prepared following the method of Preparation 23, starting from the product of Preparation 21, and using methanol as the chromatography solvent.

Mass Spectrum: M = 205.

Preparation 26

2-(2-Naphthyl)propylamine

The title compound, 450 mg (44%) was prepared as an oil following the method of Preparation 23, starting from the product of Preparation 22, and using methanol as the chromatography solvent.

Mass Spectrum: M = 185.

Preparation 27

Methyl 1-(4-*t*-butylphenyl)cyclopropanecarboxylate

4 g (19.4 mmol) of Methyl 4-tert-butylphenylacetate, 39 mL (1.0 m, 2 Eq.) of lithium bis (trimethylsilyl) amide, and 3 g (2 Eq.) of 1-bromo-2-chloroethane in 100 mL dry THF were reacted as described in Preparation 11, except that the reaction mixture was stirred for one hour at ambient temperature before work-up. This reaction yielded 4.21 g of a brown oil. This material was purified via silica gel chromatography eluting with a gradient solvent of hexanes to hexanes/EtOAc 19:1 to yield the title compound 1.57 g (35%) as a pale yellow solid m.p. 58^{o}-60^{o} C Calculated for $C_{15}H_{20}O_{2}$: Theory: C, 77.37; H, 8.81 Found: C, 77.54; H, 8.68.

Preparation 28

1-(4-*t*-butylphenyl)cyclopropanecarboxylic acid

1 g (4.3 mmol) of the product of Preparation 27 and 650 mg (15.5 mmol) of lithium hydroxide were placed in a tri-solvent solution of THF (66 mL), methanol (22 mL), and H_2O (22 mL) and reacted as described in Preparation 15

to yield 840 mg of a solid. This material was purified via silica gel chromatography eluting with hexanes/EtOAc 1:1 as a solvent to yield the title compound, 600 mg, (64%) as a white solid. m.p. dec >150^{O}C Calculated for $C_{14}H_{18}O_2$: Theory: C, 77.03; H, 8.31 Found: C, 77.08; H, 8.02.

Preparation 29

1-(4-*t*-butylphenyl)cyclopropanecarboxamide

580 mg. (2.7 mmol) of the product of Preparation 27, oxalyl chloride (10 mL), methylene chloride (10mL) and one drop DMF were reacted as described in Preparation 19 to yield 573 mg of the crude acid chloride. Amide conversion was accomplished with 28% ammonium hydroxide (10 mL) and dioxane (10 mL) as described in Preparation 27 to yield 590 mg of a solid. Trituration in hexanes/EtOAc. 19:1 and subsequent filtration yielded 510 mg (87%) of the title compound as a white solid. m.p. 178^{O}-180^{O}C Calculated for $C_{14}H_{19}NO$: Theory: C, 77.38; H, 8.81; N, 6.45 Found: C, 77.53; H, 8.77; N, 6.39.

Preparation 30

1-(4-*t*-butylphenyl)cyclopropylmethylamine

7 mL of Borane-tetrahydrofuran complex (1.0 M, 7 mmol) and 500 mg (2.3 mmol) of the product of Preparation 29 in THF (50 mL) were reacted as described in Preparation 23 to yield 510 mg of an oil. Purification was achieved via silica gel chromatography eluting with a gradient solvent of EtOAc/ methanol 9:1 to methanol to yield 222 mg (47%) as a solid, m.p. 39^{O}-41^{O}C Calculated for $C_{14}H_{21}N$: Theory C, 82.70; H, 10.41; N, 6.89 Found: C, 81.36; H, 10.13; N, 7.24.

Preparation 31

2-(4-Bromophenyl)propylamine hydrochloride

To a -15°C solution of 50.0 g (251.2 mmol) of 4-bromo-acetophenone and 49.0 g (251.2 mmol) of tosylmethyl iso-cyanide in 800 mL of dry dimethoxyethane was added a hot solution of 50.7 g (452.2 mmol) of potassium tert-butoxide in 230 mL of tert-butyl alcohol dropwise at a rate to maintain the

temperature below 0°C. The reaction was stirred at -5°C for 45 min after addition was complete. The cooling bath was removed and the reaction stirred for 2.5 h more. The mixture was concentrated *in vacuo* to a volume of 200 mL and diluted with 500 mL of water. The aqueous mixture was extracted four times with diethyl ether, and the combined organic portions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in 55 mL of tetrahydrofuran and heated to reflux. To the refluxing solution was added slowly dropwise 27.6 mL (276.3 mmol) of 10.0 M borane-dimethylsulfide complex. Refluxing was continued for 20 min after addition was complete. The mixture was cooled to ambient temperature and methanol saturated with hydrogen chloride was added very slowly until pH 2 was achieved. The mixture was concentrated *in vacuo* and the residue was dissolved in methanol and concentrated *in vacuo* again. The solid residue was suspended in 125 mL of ethanol, filtered, rinsed with ethanol then diethyl ether. The white solid was dried *in vacuo* to afford 25.4 g (40%) of the title compound. The filtrate was concentrated *in vacuo* and suspended in diethyl ether. The solid was filtered, rinsed with diethyl ether and dried *in vacuo* to afford another 15.6 g (25 %) of the title compound.

Preparation 32

2-(4-Methylphenyl)propionitrile

The title compound was prepared from 4-methylphenyl-acetonitrile as described in Preparation 7.

Analysis for $C_{10}H_{11}N$:

Theory:	C, 82.72; H, 7.64; N, 9.65.
Found:	C, 82.75; H, 7.42; N, 9.94.

Preparation 33

2-(4-Methylphenyl)propylamine hydrochloride

The title compound was prepared from the product of Preparation 32 as described in Preparation 8.

Field Desorption Mass Spectrum: M = 150 (M-HCl)

Preparation 34

2-(4-Benzyloxyphenyl)propionitrile

4-Hydroxyphenylacetonitrile (15.3 g, 114.9 mmol) was dissolved in dimethylformamide (120 mL) and to this was added potassium carbonate (23.78 g, 172.4 mmol), benzyl bromide (20.64 g, 120.6 mmol) and potassium iodide (3.81 g, 30.0 mmol). The solution was stirred at ambient temperature for 6 hours after which water was added. 4-Benzyloxyphenyl-acetonitrile precipitated out of solution. The suspension was filtered and the precipitate washed with water (3x). Yield 24.8 g (97%) as yellow crystals. The title product was prepared from 4-benzyloxyphenyl-acetonitrile as described in Preparation 7. Yield 76%.

Field Desorption Mass Spectrum: M = 237.2.

Analysis for $C_{16}H_{15}NO$:

Theory:	C, 80.98; H, 6.37; N, 5.90.
Found:	C, 80.93; H, 6.46; N, 6.11.

Preparation 35

2-(4-Benzyloxyphenyl)propylamine hydrochloride

The title compound was prepared from the product of Preparation 34 as described in Preparation 2.

Analysis for $C_{16}H_{20}ClNO$:

Theory:	C, 59.55; H, 8.00; N, 6.94.
Found:	C, 59.33; H, 7.89; N, 6.71.

Preparation 37

2-(4-bromophenyl)-1-nitro-1-methylethylene

A solution of 30.0 g (162 mmol) of 4-bromobenzaldehyde, 116 mL (1.6 mole) of nitroethane, and 37.5 g (486 mmol) of ammonium acetate in 200 mL of toluene was heated under a Dean and Stark trap for 18 hours. The mixture was then cooled to 80°C, 1 mL of concentrated sulfuric acid was added, and the mixture was stirred at 80°C for 2 hours. The mixture was then cooled to ambient temperature and washed with 200 mL of brine. The organic layer was separated and the aqueous layer was extracted three times with 60 mL of diethyl ether.

The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was recrystallized from methanol to afford 18.7 g (47%) of the title compound.

Preparation 38

2-(4-bromophenyl)-1-nitro-1-methylethane

A suspension of 1.3 g (33.9 mmol) of lithium aluminum hydride in 55 mL of tetrahydrofuran (THF) was cooled to 0°C. A solution of 4.1 g (16.9 mmol) of material from Preparation 37 in 5 mL of THF was added dropwise. 1.3 mL of water, 1.3 mL of 1M sodium hydroxide and 4.0 mL of water were added in sequence. The mixture was filtered through Celite and rinsed with dichloromethane. The organics were concentrated in vacuo to afford 3.0 g of the title compound (83%).

Preparation 41

2-(4-bromophenyl)-N-(t-butoxycarbonyl)ethylamine

To a room temperature solution of 10.0 g (50.0 mmol) of 4-bromophenethylamine and 11.0 g (50.0 mmol) of di-tert-butyl dicarbonate in 100 mL of chloroform was added 100 mL of saturated aqueous sodium bicarbonate. The mixture was stirred at room temperature for 1.5 hours and diluted with 100 mL of water. The organic layer was separated and the aqueous layer was extracted two times with 100 mL each of chloroform. The combined organics were washed once with 100 mL of 10% aqueous sodium bisulfate, dried ($NaSO_4$), filtered and concentrated *in vacuo* to afford 14.6 g (97%).

Mass Spectrum: M+1 = 301.

Preparation 42

4-cyanophenylboronic acid

A solution of 10.0 g (54.9 mmol) of 4-bromobenzonitrile in 100 mL of tetrahydrofuran was cooled to -85°C whereupon 36.0 mL (57.6 mmol) of 1.6 M solution of n-butyllithium in hexanes was added. The mixture was stirred for five minutes and 19.0 mL (82.4 mmol) of triisopropylborate was added. The mixture

was stirred at -85°C for 30 minutes then warmed to ambient temperature over one hour. To the mixture was added 35 mL of 5 N hydrochloric acid and stirring was continued for 2.5 hours. The mixture was diluted with 100 mL of saturated aqueous sodium chloride and extracted three times with 100 mL each of ethyl ether. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallized from water and filtered to afford 2.0 g (25%) of the title compound.

Preparation 45

Dibromoformaldoxime

A solution of 150 g (1.6 mole) of glyoxylic acid and 142 g (2.0 mole)of hydroxylamine hydrochloride in 1200 mL of water was stirred for 2 days. To the mixture was added slowly 342 g (4.1 mole) of sodium bicarbonate and 1000 mL of dichloromethane. The mixture was cooled to 0°C and a solution of 147 mL (2.8 mole) bromine in 700 mL of dichloromethane was added dropwise. The mixture was stirred at ambient temperature for 18 hr. The organic layer was separated and the aqueous layer was extracted three times with 300 mL each of dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to afforded 93.1 g (28%) of the title compound.

Preparation 46

2-trimethylstannylthiazole

A. To a -78°C solution of 5.0 g (58.7 mmol) of thiazole in 120 mL of tetrahydrofuran was added of 36.7 mL (58.7 mmol) of a 1.6 M solution of n-butyllithium in hexanes. The mixture was stirred for 20 minutes whereupon 11.7 g (58.7 mmol) in 15 mL of tetrahydrofuran was added dropwise over 15 minutes. The cooling bath was removed and the mixture was stirred for two hours. The mixture was diluted with 100 mL of water and extracted three times with 100 mL ethyl ether. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in 50 mL of ethyl ether, filtered through silica gel and concentrated *in vacuo* to afford 3.6 g (24%) of the title compound.

Preparation 49

4-(4-Bromophenyl)-1,1-dioxotetrahydro-1,2-thiazine

A. Ethyl 4-bromophenylacetate: A solution of 25.0 g (116.3 mmol) of 4-bromophenylacetic acid, 24.1 g (174.4 mmol) of potassium carbonate and 10.2 mL (127.9 mmol) of iodoethane in 250 mL of acetonitrile was heated at 70°C for 16 hours. The mixture was cooled to ambient temperature, diluted with 200 mL of ethyl acetate and washed once with 200 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted three times with 75 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 16.2 g (57%) of the title compound.

B. Phenyl 3-carbethoxy-3-(4-bromophenyl)propyl-sulfonate: A solution of 16.2 g (66.6 mmol) of material from Step A, 4.6 g (33.3 mmol) of potassium carbonate and 4.4 g (16.7 mmol) of 18-crown-6 in 130 mL of toluene was heated to 90°C and 6.1 g (33.3 mmol) of phenyl vinylsulfonate in 35 mL of toluene was added dropwise over one hour. The mixture was heated for 16 hours, cooled to ambient temperature and diluted with 100 mL of ethyl acetate. The mixture was washed once with 100 mL of half saturated brine. The organic layer was separated and the aqueous layer was extracted once with 50 mL of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (Waters 2000, 15% ethyl acetate/hexanes) of the residue affords 4.8 g (17%) of the title compound.

Analysis calculated for $C_{18}H_{19}O_5SBr$: %C, 50.59; %H, 4.48. Found: %C, 50.61; %H, 4.47.

Mass Spectrum: M+1 = 428.

C. Phenyl 3-carboxy-3-(4-bromophenyl)propylsulfonate: To a solution of 4.8 g (11.3 mmol) of material from Step B in 40 mL of methanol was added 6.8 mL of 2 N aqueous sodium hydroxide. The mixture was stirred at ambient temperature for 5 hours and concentrated *in vacuo*. The residue was dissolved in 50 mL of water and extracted three times with 20 mL each of ethyl ether. The aqueous layer is acidified to pH 2 with 10% aqueous sodium bisulfate and extracted four times with 20 mL each of ethyl acetate. The combined ethyl acetate layers were

dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 4.1 g (91%) of the title compound.

Analysis calculated for $C_{16}H_{15}O_5SBr$: %C, 48.13; %H, 3.79. Found: %C, 48.17; %H, 3.53.

Mass Spectrum: M = 399.

D. Phenyl 3-carboxamido-3-(4-bromophenyl)propyl-sulfonate: To a 0°C solution of 4.1 g (10.2 mmol) of material from Step C and 2.0 mL (14.3 mmol) of triethylamine in 23 mL of tetrahydrofuran was added 1.9 mL (14.3 mmol) of isobutyl chloroformate. The mixture was stirred at 0°C for 25 minutes whereupon 11.2 mL (22.4 mmol) of a 2 N solution of ammonia in methanol was added. The cooling bath was removed and the mixture stirred for 16 hours. The mixture was diluted with 50 mL of ethyl acetate and washed once with 50 mL of water. The organic layer was separated and the aqueous layer was extracted three times with 25 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (250 g silica gel, 35% acetone/hexanes) of the residue affords 1.7 g (44%) of the title compound.

Mass Spectrum: M = 398.

E. 4-(4-Bromophenyl)-1,1,3-trioxotetrahydro-1,2-thiazine: To a 0°C solution of 9.0 mL (9.0 mmol) of a 1.0 M tetrahydrofuran solution of potassium tert-butoxide in 15 mL of tetrahydrofuran was added a solution of 1.7 g (4.5 mmol) of material from Step D in 14 mL of tetrahydrofuran dropwise over 30 minutes. After stirring at 0°C for two hours, the cooling bath was removed and stirring continued for 30 minutes. The mixture was diluted with 25 mL of water and extracted two times with 10 mL each of ethyl ether. The aqueous portion was acidified to pH 2 with 10% aqueous sodium bisulfate and extracted four times with 20 mL each of ethyl acetate. The combined ethyl acetate layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (75 g silica gel, 0.25% acetic acid/40% acetone/hexanes) of the residue affords 0.2 g (17%) of the title compound.

Analysis calculated for $C_{10}H_{10}NO_3SBr$: %C, 39.49; %H, 3.31; %N, 4.61. Found: %C, 39.74; %H, 3.23; %N, 4.42.

Mass Spectrum: M = 304.

F. To a suspension of 0.13 g (0.4 mmol) of material from Step E and 0.2 g (4.9 mmol) of sodium borohydride in 3 mL of dioxane was added 0.4 mL (4.9 mmol) of trifluoroacetic acid slowly via syringe. After stirring at ambient temperature for 30 minutes the mixture was heated to reflux for 5 hours. The mixture was cooled to ambient temperature, diluted with 3 mL of methanol and stirred for 16 hours. The mixture was removed and stirring continued for 30 minutes. The mixture was concentrated *in vacuo*, dissolved in 10 mL of ethyl acetate and washed two times with 5 mL each of 1 N hydrochloric acid and once with 5 mL of 20% saturated aqueous sodium bicarbonate/brine. The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 0.1 g (89%) of the final title compound.

Analysis calculated for $C_{10}H_{12}NO_3SBr$: %C, 41.39; %H, 4.17; %N, 4.83. Found: %C, 41.10; %H, 4.34; %N, 4.76.

Mass Spectrum: M - 1 = 289.

Preparation 50

D,L-penicillamine methyl ester hydrochloride

Through a suspension of 10.0 g (67.0 mmol) of D,L-penicillamine in 200 mL of methanol was bubbled hydrogen chloride for 5 minutes. The mixture was refluxed for 16 hours, cooled to ambient temperature and concentrated *in vacuo* The residue was suspended in ethyl ether, filtered and dried to afford 12.6 g (94%) of the title compound.

Mass Spectrum: M = 163.

Preparation 51

N-(t-butoxycarbonyl)-4-tributylstannylaniline

A. N-(t-Butoxycarbonyl)-4-bromoaniline: To a solution of 6.0 g (39.4 mmol) of 4-bromoaniline in 30 mL of tetrahydrofuran was added 69.8 mL (69.8 mmol) of a 1.0 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran. To the mixture was added 7.6 g (34.9 mmol) of di-t-butyldicarbonate in 10 mL of tetrahydrofuran. The mixture was stirred at ambient temperature for one hour and concentrated *in vacuo*. The residue was dissolved in 50 mL of ethyl acetate

and washed once with 50 mL of 10% aqueous sodium bisulfate. The organic layer was separated and the aqueous layer was extracted two times with 25 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (250 g of silica gel, 10% ethyl acetate/hexanes) of the residue afforded 5.0 g (53%) of the title compound. Analysis calculated for $C_{11}H_{14}NO_2Br$: %C, 48.55; %H, 5.19; %N, 5.15. Found: %C, 48.81; %H, 5.29; %N, 4.95.

Mass Spectrum: M -1 = 271.

B. A degassed solution of 4.9 g (18.0 mmol) of material from Step A, 2.6 mL (18.9 mmol) of triethylamine, 9.6 mL (18.9 mmol) of bis(tributyltin) and 1.0 g (0.9 mmol) of tetrakis(triphenylphosphine)palladium(0) in 45 mL of toluene was heated to 100°C for 5 hours . The mixture was cooled to ambient temperature and diluted with 40 mL of ethyl acetate. The mixture was washed once with 50 mL of 10% aqueous sodium bisulfate, the organics separated and the aqueous layer extracted three times with 20 mL each of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (400 g of silica gel, 5% ethyl acetate/hexanes) of the residue afforded 1.4 g (16%) of the final title compound.

Mass Spectrum: M +1 = 483.

Preparation 53

N-2-(4-(3-thienyl)phenyl)propyl amine

A. 2-(3-thienyl)phenyl-N-(t-butoxycarbonyl)propyl amine: To a solution of 0.7 g (2.2 mmol) of material from Preparation 4, 0.3 g (2.4 mmol) thiophene-3-boronic acid and 0.46 g (3.3 mmol) of potassium carbonate in 5 mL of dioxane and 1 mL of water was added 0.025 g (0.11 mmol) of palladium(II)acetate and 0.058g (0.22 mmol) triphenylphosphine. The mixture was heated at 100 °C for 18 hr. The mixture was cooled to room temperature and 5 mL of brine was added. The organic layer was separated and dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (25 g of silica gel, 25% ethyl acetate/hexanes) of the residue afforded 0.44 g (60%) of the title compound.

B. A solution of 0.4 g (1.3 mmol) of material from Preparation 53A in 4 mL of dichloromethane and 1 mL of trifluoroacetic acid was stirred at ambient temperature for 3 hr. The mixture was concentrated in vacuo and the residue was dissolved in 5 mL ethyl acetate and 5 mL saturated sodium bicarbonate. The organic layer was separated and the aqueous layer extracted three times with 5 mL of ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo to afford 0.21 g (74%) of the title compound.

Preparation 54A

4-(N,N-dibenzylamino)phenylacetonitrile

A solution of 4-aminophenylacetonitrile (20 g, 151.3 mmol) in dry DMF (150 ml) was treated with potassium carbonate (50.1 g, 363.1 mmol), benzyl bromide (54.4 g, 318 mmol), and potassium iodide (5 g, 0.2 30.3 mmol). The reaction mixture was stirred at room temperature for 12 h. Water (100 mL) was added to the mixture and the organic was extracted with ether (3x200 mL). The combined organic fraction was washed with brine (200 mL), dried over sodium sulfate and concentrated. The crude product was further purified by flash chromatography (SiO_2, 20% EtOAc:Hexanes) to give 36.2 g (76%) of the pure product. THE NMR SPECTRUM was consistent with the proposed title structure. Field Desorption Mass Spectrum :M^+ = 312.

Preparation 55

2-(4-(N,N-dibenzylamino)phenyl)propionitrile

A -78°C solution of the material from Preparation 54A (22.8 g, 73 mmol) in dry THF (70 mL) was treated with lithium bis(trimethylsilyl)amide (1M in THF, 76.6 mL, 76.6 mmol). The resulting mixture was stirred at -78 °C for 1h. Methyl iodide (4.8 mL, 76.6 mmol) was added to the mixture. The reaction mixture was stirred at -78 °C for 1 h and gradually was allowed to warm to room temperature over 12 h. Hydrochloric acid (0.2 M, 100 mL) was added to the mixture and the organic layer was extracted with ether (3x200 mL). The combined organic fraction was washed with water (3X200 mL), brine (200 mL), dried over sodium sulfate and concentrated. The crude product was further purified by flash

chromatography (SiO_2, 20% EtOAc: Hexanes) to give 22.6 g (95%) of the pure product. The NMR spectrum was consistent with the proposed title structure. Field Desorption Mass Spectrum :M^+ = 326.

Preparation 56

2-(4-(N,N-dibenzylamino)phenyl)propylamine hydrochloride

A 0°C solution of the material from Preparation 55 (23.6 g, 72.3 mmol) in dry THF (100 mL) was treated with borane methylsulfide (10 M in THF, 8 mL, 80 mmol). The reaction mixture was stirred while refluxing for 3 h. The solution was cooled down to room temperature and was treated with a saturated solution of hydrochloric acid in methanol until a white precipitate formed. The solvent was removed in vacuo and the resulting white solid was triturated with ether (4x100 mL). The desired hydrochloric salt was dried under vacuo to give 28.2 g (97%) of the pure product which was used in next step without any further purification. The NMR spectrum was consistent with the proposed title structure.

Preparation 61

2-(4-nitrophenyl)propionitrile

A -15°C solution of 4-nitroacetophenone (16.5 g, 100 mmol) and tosylmethyl isocyanide (29.3 g, 150 mmol) in methoxyethyl ether (400 mL) was slowly treated with a room temperature solution of the potassium *t*-butoxide (28 g, 250 mmol) in t-butanol (200 mL). The reaction mixture was stirred at -15 °C for 1 h and then allowed to warm to room temperature over night. Water (100 mL) was added to the mixture and organic was extracted with ether (3X200 mL). The combined organic fraction was washed with water (3X200 mL), brine (100 mL), dried over sodium sulfate, and concentrated *in vacuo* to give the crude material which was further purified by flash chromatography (SiO_2, 30% EtOAc: Hexanes) to give 13.6 g (77%) of the title compound. The NMR spectrum was consistent with the proposed title structure. Field Desorption Mass Spectrum :M^+ = 225.

Preparation 62

2-(4-nitrophenyl)propylamine

A 0°C solution of the material from Preparation 61 (11.8 g, 67 mmol) in dry THF (200 mL) was treated with borane tetrahydrofuran (1 M in THF, 72 mL, 72 mmol). The reaction mixture was stirred at room temperature for 16 h. A solution of THF:MeOH (1:1, 10 mL)and sodium hydroxide (5 N, 40 mL) were added to the reaction mixture stepwise and the mixture was refluxed for 5 h. The reaction mixture was allowed to cool to room temperature. Organic was extracted with dichloromethane (3X100 mL). The combined organic fraction was washed with water (3X200 mL), brine (100 mL), dried over potassium carbonate, and concentrated *in vacuo* to give the crude material which was further purified by flash chromatography (SiO_2, 5% MeOH: CH_2Cl_2) to give 8.5 g (71%) of the pure product. The NMR spectrum was consistent with the proposed title structure. Field Desorption Mass Spectrum :M^+ = 181.

Preparation 68

N-*t*-butyloxycarbonyl-4-piperazinoacetophenone

A solution of the 4-piperazinoacetophenone (10 g, 49 mmol) in tetrahydrofuran:water (200 mL, 1:1 mixture) was treated with potassium carbonate (8.43 g, 58 mmol) and di-*t*-butyl dicarbonate (13.1 g, 53.9 mmol). The reaction mixture was stirred at room temperature for 3 h. Water (300 mL) was added to the mixture and the organic layer was extracted with ethyl acetate (3X100 mL). The combined organic fraction was washed with water (2X200 mL), brine (100 mL), dried over sodium sulfate, and concentrated in vacuo to 17. 41 g of the yellowish solid. The crude product was further purified by Prep LC 2000 eluting with 30% EtOAc:Haxanes to give 10.9 g (73%) of the title compound as a white solid. Field Desorption Mass Spectrum :M^+ = 305.

Preparation 69

2-(N-*t*-butyloxycarbonyl-4-piperazinophenyl)propionitrile

The title compound 1.8g (16%) was prepared as a solid following the method of Preparation 61, starting from the product of Preparation 68 and using

tosylmethyl isocyanide. The NMR spectrum was consistent with the proposed title structure. Field Desorption Mass Spectrum :M^+ = 316.

Preparation 70

2-(N-*t*-butyloxycarbonyl-4-piperazinophenyl)propylamine

The title compound 1.78g (100%) was prepared as a solid following the method of Preparation 62, starting from the product of Preparation 69 and using borane methylsulfide. The NMR spectrum was consistent with the proposed title structure. Field Desorption Mass Spectrum :M^+ = 319.

Preparation 74

3-Tributyltin-2-cyclopenten-1-one

A -20°C solution of hexabutylditin (4.6 g, 7.9 mmol) in dry THF (15 mL) was treated with nBuLi (4.9 mL, 7.9 mmol, 1.6 M solution in hexanes). The reaction mixture was stirred at -20°C for 30 minutes and then cooled to -78°C. The mixture was treated with 3-ethoxy-2-cyclopenten-1-one (1.0 g, 7.9 mmol) and the reaction mixture stirred at -78°C for 30 minutes. A saturated, aqueous solution of ammonium chloride (2 mL) followed by water (30 mL) and the organic extracted with hexanes (2X30 mL). The combined organic layers were washed with brine (20 mL) , dried over magnesium sulfate and concentrated *in vacuo.* This gave 2.7 g (93%) of the crude product which was used without further purification. The NMR spectrum was consistent with the title structure.

Preparation 76

1-(4-bromophenyl)-2,5-dimethylpyrrole

4-Bromoaniline (56.0 g., 0.33 Mol.), 2,5-hexanedione (37.6 g., 0.33 Mol), and acetic acid (5mL) were placed into Toluene (500 mL) and heated under reflux for 8 hours employing a dean stark trap to remove the water from the reaction. The reaction was cooled to room temperature and concentrated under reduced vacuum. The resulting oil was taken into ethyl acetate, washed one time each with 2N hydrochloric acid, 2N NaOH, and H_2O, dried over Na_2SO_4, and concentrated under reduced vacuum to yield a brown solid. The material

was purified by silica gel flash chromatography eluting with hexanes. Concentration of the appropriate fractions yielded 55.0 gm. of a light yellow solid. (68%) The NMR spectrum was consistent with the proposed title structure. Field Desorption Mass Spectrum :M^+ 249 m.p. 71°-73° C

Preparation 77

1-(4-acetylphenyl)-2,5-dimethylpyrrole

A -30° C solution of the material from Preparation 76 (25.0 g, 0.1 mol) in dry ether (500 mL) was treated with n-butyllithium (70 mL of 1.6 M, 0.12 mol) and stirred for one hour at -30°C. N,N Dimethyl acetamide (9.7 g, 0.12 mol) was added and the reaction continued at this temperature for 4 hours. The reaction was then allowed to warm to room temperature and stirred over night at this temperature. In the morning, the mixture was diluted with ethyl acetate and the combined organic layers were washed one time each with 2.0 N hydrochloric acid and H_2O, dried over Na_2SO_4, and concentrated under reduced vacuum to yield a white solid. The material was triturated in hexanes and filtered to yield 12.8 gm. of a white solid. m.p. 106°-108° C (60%) THE NMR SPECTRUM was consistent with the proposed title structure. Field Desorption Mass Spectrum : M^+ 214

Preparation 78

1-(4-(1-cyano)ethylphenyl)-2,5-dimethylpyrrole

The starting ketone from Preparation 77 (44.3 g, 0.21 mol), tosylmethyl isocyanide (40.6 g, .21 mol), potassium-t-butoxide (39.2 g, 0.35 mol), and t-butyl alcohol (250 mL) were reacted in ethylene glycol dimethyl ether (500 mL) as described in Preparation 61 to yield a yellow solid. Purification was achieved by silica gel flash chromatography eluting with hexanes/ethyl acetate 4:1 to yield 32.3 gm. of yellow crystals. m.p. 79°-80° C (68%) Field desorption Mass Spectrum: M^+ 225

Preparation 79

1-(4-(2-(2-cyano)propyl)phenyl)-2,5-dimethylpyrrole

A -78° C solution of material from Preparation 78 (7.0 g, 32 mmol) in dry tetrahydrofuran (100 mL) was treated with lithium (bis)trimethylsilylamide (40 mL of 1.0M, 1.3 eq.). After stirring 30 minutes at this temperature, methyl iodide (2.6 mL, 1.3 eq.) was added dropwise and the reaction was allowed to warm to room temperature. The mixture was diluted with ether and the combined organic layers were washed once with H_2O, dried over K_2CO_3, and concentrated under reduced vacuum to yield 7.61 gm. of a yellow solid. Material was purified via silica gel chromatography eluting with a solvent of hexanes/ethyl acetate 9:1 to yield 6.30 gm. of a yellow solid. m.p. 135°-137° C (83%). Field desorption Mass Spectrum: M^{+}+1 239

Preparation 80

1-(4-(2-(3-amino-2-methyl)propyl)phenyl-2,5-dimethylpyrrole

The nitrile from Preparation 79 (6.23 g, 26.2 mmol) in tetrahydrofuran (250 mL) was treated with borane-THF complex (17.1 mL, 1.0 M) as described in Preparation 62 to yield 6.37 gm. of a foam. This material was purified via silica gel chromatography eluting with a gradient solvent of dichloromethane to dichloromethane/methanol 9:1 to yield 4.08 gm. of a white solid. m.p. 95°-97° C (65%). The NMR spectrum was consistent with the proposed title structure. Field Desorption Mass Spectrum : M^{+} 243

Preparation 85

4-Bromophenylacetyl chloride

A solution of 50.0 g (232 mmol) of 4-bromophenyl-acetic acid in 150 mL of thionyl chloride was stirred at room temperature for 18 hr. The mixture was concentrated *in vacuo* to afford 54 g (100%) of the title compound.

Preparation 86

(R)-(-)-4-Benzyl-3-(4-bromophenylacetyl)-2-oxazolidinone

A solution of 20.0 g (117 mmol) of (R)-(+)-4-benzyl-2-oxazolidinone in 300 mL of tetrahydrofuran was cooled to -78°C and 73.0 mL (117 mmol) of 1.6M n-Butyllithium was added dropwise. The mixture was stirred 30 min then was slowly added via cannula to a solution of 25 g (107 mmol) of material from Preparation 85 in 150 mL of tetrahydrofuran at -78°C. The mixture was stirred for 1 hr and then 300 mL of 10% aqueous sodium bisulfate was added. The organic layer was separated and the aqueous layer was extracted three times with 100 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (750 g of silica gel, 25% ethyl acetate/hexanes) of the residue afforded 27.4 g (68%) of the title compound.

Analysis calculated for $C_{18}H_{16}BrNO_3$: %C, 57.77; %H, 4.31; %N, 3.74. Found: %C, 57.62; %H, 4.21; %N, 3.74.

Field Desorption Mass Spectrum: M = 374.

$[\alpha]_D^{20}$ = -59.83 (c=1.04, $CHCl_3$).

Preparation 87

(-)-4*R*-Benzyl-3-(2*R*-(4-bromophenyl)propionyl)-2-oxazolidinone

A solution of 48 g (128 mmol) of material from Preparation 86 in 200 mL of tetrahydrofuran was cooled to -78 °C and 141 mL (141 mmol) of 1M sodium bis(trimethyl-silyl)amide was added dropwise. The mixture was stirred 60 min then a solution of 20 g (141 mmol) of iodomethane in 20 mL of tetrahydrofuran was slowly added. The mixture was stirred for 60 min at -78°C and then allowed to warm to room temperature for 60 min. To the reaction was added 10% aqueous sodium bisulfate and the organic layer was separated and the aqueous layer was extracted three times with 100 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (500 g of silica gel, 25% ethyl acetate/hexanes) of the residue afforded 28.7 g (58%) of the title compound.

Analysis calculated for $C_{19}H_{18}BrNO_3$: %C, 58.78; %H, 4.67; %N, 3.61. Found: %C, 58.81; %H, 4.63; %N, 3.54.

Field Desorption Mass Spectrum: M = 388.

$[\alpha]_D^{20}$ = -110.4 (c=0.96, $CHCl_3$).

Preparation 88

(R)-(+)-2-(4-bromophenyl)propanol

A solution of 28.7 g (74 mmol) of material from Preparation 87 in 250 mL of ether was cooled to 0°C and 74 mL (148 mmol) of 2M lithiumborohydride in tetrahydrofuran was added dropwise. The mixture was stirred for 2 hr then 1N sodium hydroxide was added and the mixture was stirred until both organic and aqueous layers became clear. The organic layer was separated and the aqueous layer was extracted three times with 10 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (800 g of silica gel, 25% ethyl acetate/hexanes) of the residue afforded 12.3 g (79%) of the title compound.

Analysis calculated for $C_9H_{11}BrO$: %C, 50.26; %H, 5.15. Found: %C, 48.96; %H, 4.91.

Field Desorption Mass Spectrum: M+1 = 216.

$[\alpha]_D^{20}$ = +13.79 (c=1.06, $CHCl_3$).

Preparation 90

(R)-2-(4-bromophenyl)propyl azide

A solution of 15.8 g (54 mmol) of material from Preparation 89 in 180 mL of N,N-dimethylformamide and 7.0 g (108 mmol) sodium azide was heated at 80°C for 5 hr. The mixture was cooled and concentrated in vacuo. The residue was partitioned between 100 mL of water and 100 mL of ether. The organic layer was separated and the aqueous layer was washed three times with 30 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to afforded 12.13 g (94%) of the title compound.

Preparation 91

(R)-(+)-2-(4-bromophenyl)propyl amine hydrochloride

A solution of 12.2 g (50.4 mmol) of material from Preparation 90 and 14.5 g (55.4 mmol) of triphenylphosphine in 168 mL of tetrahydrofuran and 3.6 mL of water was stirred at room temperature for 18 hr. The mixture was diluted with 100 mL of ether and 50 mL of brine. The organic layer was removed and dried (MgSO4), filtered and concentrated in vacuo. The residue was dissolved in 100 mL of ether and to this was added 200 mL of hydrochloric acid saturated ether. Filtration of the resulting solid afforded 11.9 g (94%) of the title compound.
Analysis calculated for $C_9H_{13}BrClN$: %C, 43.14; %H, 5.23; %N, 5.59. Found: %C, 43.44; %H, 5.23; %N, 5.56.
Mass Spectrum: [M-HCl] = 214.
$[\alpha]_D^{20}$ = +24.06 (c=1.00, H_2O).

Preparation 92

(R)-2-(4-bromophenyl)-N-(t-butoxycarbonyl)propyl amine

To a solution of 5.0 g (20.0 mmol) of material from Preparation 91 in 30 mL of chloroform and 30 mL of saturated sodium bicarbonate was added 4.3 g (20.0 mmol) of di-*tert*-butyl dicarbonate. The solution was stirred at room temperature for 18 hr. The organic layer was separated and the aqueous layer was extracted three times with 10 mL each of chloroform. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 6.2 g (100%) of the title compound.

Preparation 93

(S)-(+)-4-Benzyl-3-(4-bromophenylacetyl)-2-oxazolidinone

Following the procedure of Preparation 86 and using (S)-(-)-4-benzyl-2-oxazolidinone instead of (R)-(+)-4-benzyl-2-oxazolidinone afforded 25.3 g (63%) of the title compound.

Analysis calculated for $C_{18}H_{16}BrNO_3$: %C, 57.77; %H, 4.31; %N, 3.74. Found: %C, 57.69; %H, 4.18; %N, 3.82.

Field Desorption Mass Spectrum: M = 374.

$[\alpha]_D^{20}$ = +59.35 (c=1.04, $CHCl_3$).

Preparation 94

(+)-4*S*-Benzyl-3-(2*S*-(4-bromophenyl)propionyl)-2-oxazolidinone

Following the procedure of Preparation 87 and using material from Preparation 93 instead of material from Preparation 86 afforded 28.9 g (51%) of the title compound.

Analysis calculated for $C_{19}H_{18}BrNO_3$: %C, 58.78; %H, 4.67; %N, 3.61. Found: %C, 59.40; %H, 4.61; %N, 3.64.

Field Desorption Mass Spectrum: M = 388.

$[\alpha]_D^{20}$ = +114.8 (c=1.01, $CHCl_3$).

Preparation 95

(S)-(-)-2-(4-bromophenyl)propanol

Following the procedure of Preparation 88 and using material from Preparation 94 instead of material from Preparation 87 afforded 12.3 g (79%) of the title compound.

Analysis calculated for $C_9H_{11}BrO$: %C, 50.26; %H, 5.15. Found: %C, 50.38; %H, 5.08.

Field Desorption Mass Spectrum: M+1 = 216.

$[\alpha]_D^{20}$ = -13.25 (c=1.06, $CHCl_3$).

Preparation 97

(S)-2-(4-bromophenyl)propyl azide

Following the procedure of Preparation 90 and using material from Preparation 96 instead of material from Preparation 89 afforded 13.0 g (94%) of the title compound.

Preparation 98

(S)-(-)-2-(4-bromophenyl)propyl amine hydrochloride

Following the procedure of Preparation 91 and using material from Preparation 97 instead of material from Preparation 90 afforded 11.6 g (86%) of the title compound.

Analysis calculated for $C_9H_{13}BrClN$: %C, 43.14; %H, 5.23; %N, 5.59. Found: %C, 43.36; %H, 5.39; %N, 5.64.

Mass Spectrum: [M-HCl] = 214.

$[\alpha]_D^{20}$ = -25.3 (c=1.02, H_2O).

Preparation 99

(S)-2-(4-bromophenyl)-N-(t-butoxycarbonyl)propyl amine

Following the procedure of Preparation 92 and using material from Preparation 98 instead of material from Preparation 91 afforded 5.9 g (94%) of the title compound.

Preparation 100

(R)-2-(4-(3-thienyl)phenyl)-N-(t-butoxycarbonyl)propyl amine

To a solution of 2.0 g (6.4 mmol) of material from Preparation 92, 0.9 g (7.0 mmol) of thiophene-3-boronic acid and 1.3 g (9.6 mmol) of potassium carbonate in 20 mL of dioxane and 5 mL of water was added 0.4 g (0.32 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 100°C for 18 hr. The mixture was cooled to room temperature and 20 mL of water and 20 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 10 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Chromatography (150 g of silica gel, 15% ethyl acetate/hexanes) of the residue afforded 1.4 g (70%) of the title compound.

Preparation 101

(S)-2-(4-(3-thienyl)phenyl)-N-(t-butoxycarbonyl)propyl amine

Following the procedure of Preparation 100 and using material from Preparation 99 instead of material form Preparation 92 afforded 5.9 g (94%) of the title compound.

Preparation 102

2*R*-(4-(3-thienyl)phenyl)propyl amine

A solution of 1.4 g of material from Preparation 100 in 15 mL 25% trifluoroacetic acid/dichloromethane was stirred at room temperature for 3 hr. The mixture was concentrated *in vacuo* and the residue was dissolved in 20 mL of 1N sodium hydroxide and 20 mL of ethyl acetate. The organic layer was separated and the aqueous layer was extracted four times with 10 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 0.85 g (89%) of the title compound.

Preparation 103

2*S*-(4-(3-thienyl)phenyl)propyl amine

Following the procedure of Preparation 102 and using material from Preparation 101 instead of material from Preparation 100 afforded 0.9 g (94%) of the title compound.

Preparation 104

2-(4'-(2-fluorobiphenyl))ethylamine

A. (2-(4-bromophenyl)-N-(*t*-butoxycarbonyl)ethylamine: To a solution of 10.0 g (50.0 mmol) of 4-bromophenethylamine in 100 mL of chloroform and 100 mL of saturated sodium bicarbonate was added 11.0 g (50.0 mmol) of di-*tert*-butyl dicarbonate. The solution was stirred at ambient temperature for 1 hour. The organic layer was separated and the aqueous layer was extracted three times with 30 mL each of chloroform. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 15 g (100%) of the title compound.

B. 2-(4-(2-fluorophenyl)phenyl)-N-(*t*-butoxycarbonyl)-phenyl ethylamine: To a degassed solution of 7.9 g (26.2 mmol) of material from Step A, 5.5 g (39.3 mmol) of material from Preparation 3 and 5.4 g (39.3 mmol) of potassium carbonate in 90 mL of toluene was added 1.5 g (1.3 mmol) of tetrakis-(triphenylphosphine)palladium(0). The mixture was heated at 90°C for 3 hours. The mixture was cooled to ambient temperature and 90 mL of water was added. The organic layer was separated and the aqueous layer was extracted three times with 30 mL each of ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (400 g of silica gel, 15% ethyl acetate/hexanes) of the residue afforded 7.1 g of material that was triturated in hexanes to afford 3.5 g (42%) of the title compound.

C. 2-(4'-(2-fluorobiphenyl))ethylamine: A solution of 3.5 g of material from Step B in 40 mL 20% trifluoroacetic acid/dichloromethane was stirred at ambient temperature for 1 hour. The mixture was concentrated *in vacuo* to afford 3.9 g (100%) of the title compound.

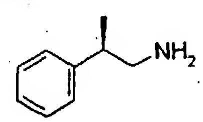
Preparation 105

Preparation of (R)-2-Phenyl-1-propylamine malate salt.

First Crop: To a mechanically stirred solution of 2-phenyl-1-propylamine amine (50.0 g, 0.370 mol, can be prepared following the procedure disclosed by A. W. Weston, A. W. Ruddy and C. M. Suter, *J. Am. Chem. Soc.* **1943**, 65, 674.) in 90% ethanol / H_2O (denatured with 0.5% toluene) (450 mL) was added L-malic acid (24.8 g, 0.185 mol) portionwise at room temperature with a 90% ethanol / H_2O rinse (50 mL) to give a clear solution after a mild exotherm. This solution was allowed to cool and a white precipitate appeared after 30 min. The precipitation was allowed to proceed with slow stirring overnight. The resulting slurry was suction filtered (buchner funnel) and rinsed with 100% ethanol (denatured with 0.5% toluene) (2 x 100 mL) to afford, after air-drying, 30 g of 2-phenyl-1-propylamine malate salt as a white solid. Chiral chromatographic analysis of the isopropylsulfonamide derivative of the free base indicated 84% ee.

Recrystallization: This 2-phenyl-1-propylamine malate salt (30 g) was suspended in 90% ethanol / H_2O (300 mL) and heated to 78 °C with slow stirring to afford a clear colorless solution. The solution was allowed to cool slowly to room temperature overnight. Precipitation commenced at 60-65 °C. The solids were filtered and rinsed at room temperature with 100% ethanol (2 x 50 mL) to give 24.3 grams (32%) of white crystalline solid. Chiral chromatographic analysis of the isopropylsulfonamide derivative of the free base indicated 96.5% ee.

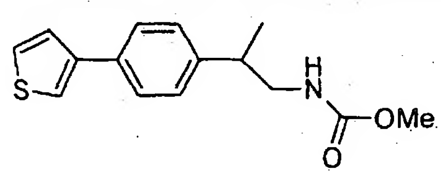
Preparation of (R)-2-phenyl-1-propylamine.



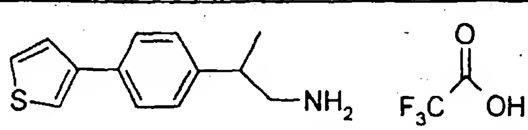
To a stirred suspension of (R)-2-phenyl-1-propylamine malate salt (24.3 g, 0.0601 mol, prepared directly above) in CH_2Cl_2 (200 mL) was added 1.0 N NaOH dropwise at room temperature. The organic phase was isolated, extracted with brine (1 x 125 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 19 g (theory: 16.3 g) of (R)-2-phenyl-1-propylamine as a clear, colorless oil.

Example 1

Preparation of 2-(4-(3-thienyl)phenyl)-N-(methyloxycarbonyl)propyl amine.



Preparation of 2-(4-(3-thienyl)phenyl)propyl amine trifluoroacetate.



A. (R)-2-(4-bromophenyl)-N-(t-butoxycarbonyl)propyl amine (12 g, 38.2 mmol, see preparation 92) was dissolved in 100 mL of dioxane:water (4:1). This

solution was treated with potassium carbonate (7.9 g, 57.3 mmol), tetrakis(triphenylphosphine)palladium (1.9 g, 1.91 mmol) and thiophene-3-boronic acid (5.4, 42 mmol). The reaction mixture was stirred at 100 °C for 12 hours. The reaction mixture was partitioned between diethyl ether and water. The organic was washed with brine, dried over sodium sulfate and concentrated in vacuo. Chromatography (SiO_2, 10-20% ethyl acetate/hexanes) gave the pure product. The resulting product was dissolved in 50 mL of dichloromethane: TFA (1:1). The mixture was stirred for 4 hours. The solvent was removed to give 8.01 g (66%) of the trifluoroacetate salt of the resulting amine.

B. A 0 °C solution of 2-(4-(3-thienyl)phenyl)propyl amine trifluoroacetate (200 mg, 0.6 mmol, prepared above) in 3 mL of dichloromethane was treated with triethylamine (263 µL, 1.9 mmol) and methyl chloroformate (58.5 µL, 0.76 mmol). The reaction mixture was stirred at room temperature for 3 hours. The crude mixture was partitioned between 30 mL of dichloromethane and water (1:1). The organic layer was extracted with dichloromethane and subsequently was washed with water, brine, dried over sodium sulfate and concentrated in vacuo. Chromatography (SiO_2, 20-30% ethyl acetate/hexanes) afforded 236 mg (86%) of the pure final title compound as a white solid.

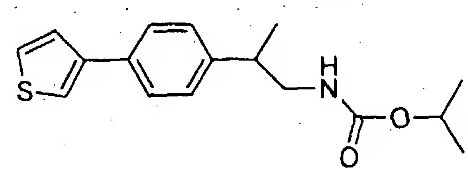
Field Desorption Mass Spectrum: 275.1

Analysis for $C_{15}H_{17}NO_2S$:

Theory:	C, 65.43; H, 6.22; N, 5.09.
Found	C, 65.61; H, 6.29; N, 5.39.

Example 2

Preparation of 2-(4-(3-thienyl)phenyl)-N-(*i*-propyloxycarbonyl)propyl amine.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl amine trifluoroacetate (prepared in example 1) and *i*-propyl chloroformate in a manner analogous to the procedure described in Example 1.

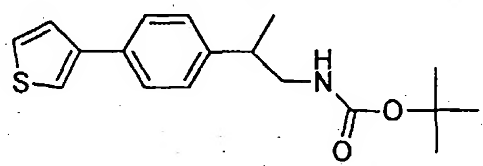
Field Desorption Mass Spectrum: 304.3

Analysis for $C_{17}H_{21}NO_2S$:

Theory:	C, 67.30;	H, 6.98;	N, 4.62.
Found	C, 67.32;	H, 6.92;	N, 4.86.

Example 3

Preparation of 2-(4-(3-thienyl)phenyl)-N-(*t*-butyloxycarbonyl)propyl amine.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl amine trifluoroacetate (prepared in example 1) and *t*-butyl chloroformate in a manner analogous to the procedure described in Example 1.

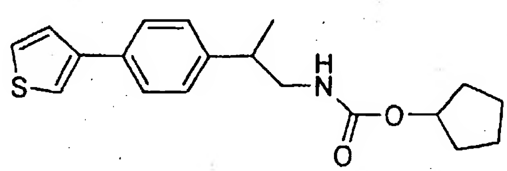
Field Desorption Mass Spectrum: 317.2

Analysis for $C_{18}H_{23}NO_2S$:

Theory:	C, 68.11;	H, 7.30;	N, 4.41.
Found	C, 68.15;	H, 7.39;	N, 4.69.

Example 4

Preparation of 2-(4-(3-thienyl)phenyl)-N-(cyclopentyloxycarbonyl) propyl-2-propylamine.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl amine trifluoroacetate (prepared in example 1) and cyclopentyl chloroformate in a manner analogous to the procedure described in Example 1.

Field Desorption Mass Spectrum: 330.2

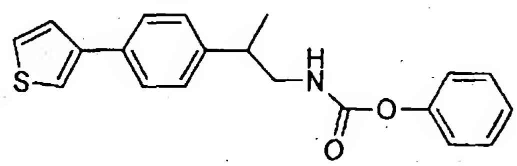
Analysis for $C_{19}H_{23}NO_2S$:

Theory: C, 69.27; H, 7.04; N, 4.25.

Found C, 69.23; H, 7.07; N, 4.50.

Example 5

Preparation of 2-(4-(3-thienyl)phenyl)-N-(phenyloxycarbonyl)propyl amine.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl amine trifluoroacetate (prepared in example 1) and phenyl chloroformate in a manner analogous to the procedure described in Example 1.

Field Desorption Mass Spectrum: 338.2

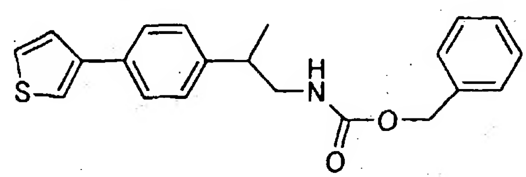
Analysis for $C_{20}H_{19}NO_2S$:

Theory: C, 71.19; H, 5.68; N, 4.15.

Found C, 71.34; H, 5.81; N, 4.39.

Example 6

Preparation of 2-(4-(3-thienyl)phenyl)-N-(benzyloxycarbonyl)propyl amine.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl amine trifluoroacetate (prepared in example 1) and benzyl chloroformate in a manner analogous to the procedure described in Example 1.

Field Desorption Mass Spectrum: 352.4

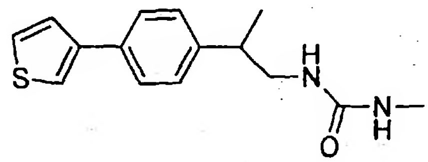
Analysis for $C_{21}H_{21}NO_2S$:

Theory: C, 71.76; H, 6.02; N, 3.99.

Found C, 71.80; H, 6.02; N, 4.24.

Example 7

Preparation of N-(2-(4-(3-thienyl)phenyl)propyl)- N'-methyl urea.



A 0 °C solution of 2-(4-(3-thienyl)phenyl)propyl amine trifluoroacetate (200 mg, 0.6 mmol, prepared in example 1) in 3 mL of dichloromethane was treated with triethylamine (263 µL, 1.9 mmol) and methyl isocyanate (53 µL, 0.9 mmol). The reaction mixture was stirred at room temperature for 3 hours. The crude mixture was partitioned between 30 mL of dichloromethane and water (1:1). The organic was extracted with dichloromethane and subsequently was washed with water, brine, dried over sodium sulfate and concentrated in vacuo. Chromatography (SiO_2, 20-30% ethyl acetate/hexanes) afford 253 mg (92%) of the pure product as a white solid.

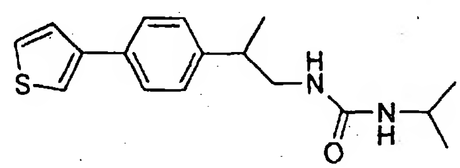
Field Desorption Mass Spectrum: 275.3

Analysis for $C_{15}H_{18}N_2OS$:

Theory:	C, 65.66; H, 6.61; N, 10.21.
Found	C, 65.54; H, 6.72; N, 10.10.

Example 8

Preparation of N-(2-(4-(3-thienyl)phenyl)propyl)- N'-*i*-propyl urea.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl-2-propyl amine trifluoroacetate (prepared in example 1) and *i*-propyl isocyanate in a manner analogous to the procedure described in Example 7.

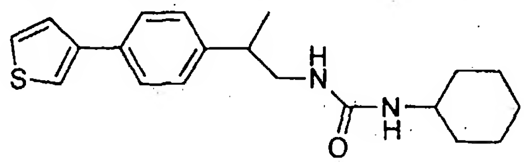
Field Desorption Mass Spectrum: 303.2

Analysis for $C_{17}H_{22}N_2OS$:

Theory:	C, 67.51; H, 7.33; N, 9.23.
Found	C, 67.63; H, 7.25; N, 9.43.

Example 9

Preparation of N-(2-(4-(3-thienyl)phenyl)propyl)- N'-cyclohexyl urea.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl-2-propyl amine trifluoroacetate (prepared in example 1) and cyclohexyl isocyanate in a manner analogous to the procedure described in Example 1.

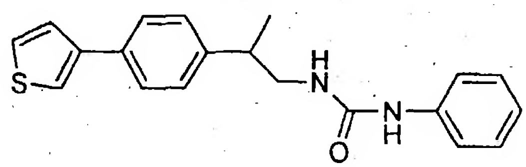
Field Desorption Mass Spectrum: 343.1

Analysis for $C_{20}H_{26}N_2OS$:

Theory:	C, 70.14; H, 7.65; N, 8.18.
Found	C, 69.49; H, 8.95; N, 10.17.

Example 10

Preparation of N-(2-(4-(3-thienyl)phenyl)propyl)- N'-phenyl urea.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl-2-propyl amine trifluoroacetate (prepared in example 1) and phenyl isocyanate in a manner analogous to the procedure described in Example 1.

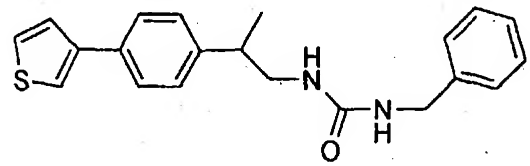
Field Desorption Mass Spectrum: 337.2

Analysis for $C_{19}H_{20}N_2OS$:

Theory:	C, 71.40; H, 5.99; N, 8.33.
Found	C, 71.18; H, 6.20; N, 8.57.

Example 11

Preparation of N-(2-(4-(3-thienyl)phenyl)propyl)- N'-benzyl urea.



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propyl-2-propyl amine trifluoroacetate (prepared in example 1) and benzyl isocyanate in a manner analogous to the procedure described in Example 1.

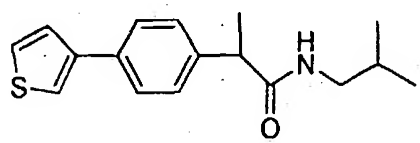
Field Desorption Mass Spectrum: 351.5

Analysis for $C_{21}H_{22}N_2OS$:

Theory:	C, 71.99;	H, 6.33;	N, 7.99.
Found	C, 72.18;	H, 6.53;	N, 8.30.

Example 12

Preparation of N-2-methylpropyl-2-(4-(3-thienyl)phenyl)propionamide.



A. 2-(4-bromophenyl)propionic acid: A mixture of 2-(4-bromophenyl)propionitrile 20.0 g (95.2 mmol, see preparation 1) and 200 mL of 6 N hydrochloric acid was refluxed for 16 hours. The cooled mixture was concentrated *in vacuo*. To the residue was added 200 mL of ether and the suspension was again concentrated *in vacuo* to afford 16.0 g (73%) of -(4-bromophenyl)propionic acid.

B. N-2-methylpropyl-2-(4-bromophenyl)2-methylacetamide: To a 0°C solution of 2-(4-bromophenyl)propionic acid1.0 g (4.4 mmol, part A above) and 0.5 g (4.8 mmol) of N-methylmorpholine in 12 mL of dichloromethane was added 0.6 g (4.6 mmol) of isobutylchloroformate and the mixture was stirred for 20 minutes. To this mixture was added 0.4 g (4.8 mmol) of isobutylamine and the mixture was allowed to warm to room temperature over 90 minutes. The reaction mixture was washed once with 10 mL of 10% aqueous sodium bisulfate and once

with saturated aqueous sodium bicarbonate. The organic portion was dried (Na_2SO_4), filtered and concentrated *in vacuo* to 1.2 g (92%) of N-2-methylpropyl-2-(4-bromophenyl)2-methylacetamide.

Analysis calculated for $C_{13}H_{18}NOBr$: %C, 54.94; %H, 6.38; %N, 4.93. Found: %C, 55.10; %H, 6.45; %N, 4.65.

Electrospray Mass Spectrum: M = 284.

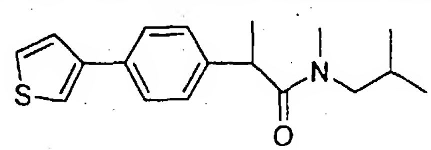
C. To a solution of N-2-methylpropyl-2-(4-bromophenyl)2-methylacetamide 1.1 g (3.9 mmol, part B above), 0.7 g (5.8 mmol) of thiophene-3-boronic acid and 0.8 g (5.8 mmol) of potassium carbonate in 12 mL of 3:1 dioxane/water was added 0.2 g (0.2 mmol) of tetrakis(triphenylphosphine)palladium. The mixture was heated to reflux for 16 hours, cooled and diluted with 10 mL of water. The mixture was extracted three times with 10 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo.* Chromatography (65 g of silica gel, 35% ethyl acetate/hexanes) of the residue afforded 0.3 g (31%) of the final title compound.

Analysis calculated for $C_{17}H_{21}NOS$: %C, 71.04; %H, 7.36; %N, 4.87. Found: %C, 70.92; %H, 7.39; %N, 4.81.

Electrospray Mass Spectrum: M+1 = 288.

Example 13

Preparation of N-methyl-N-(2-methylpropyl)-2-(4-(3-thienyl)phenyl)propionamide.



To a room temperature solution of 0.3 g (1.0 mmol) of N-2-methylpropyl-2-(4-(3-thienyl)phenyl)propionamide (prepared in example 12) in 5 mL of dimethylformamide was added 1.1 mL (1.1 mmol) of 1.0 M sodium bis(trimethylsilyl)amide in tetrahydrofuran. The mixture was stirred for 10

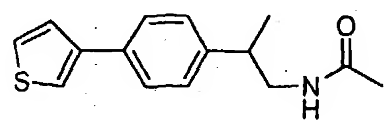
minutes whereupon 0.2 g (1.1 mmol) of iodomethane was added and the mixture stirred at room temperature for 16 hours. The mixture was diluted with 5 mL of water and extracted three times with 5 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography (10 g silica gel, 20% ethyl acetate/hexanes) afforded 0.2 g (75%) of the title compound.

Analysis calculated for $C_{18}H_{23}NOS$: %C, 71.72; %H, 7.69; %N, 4.65. Found: %C, 71.53; %H, 7.76; %N, 4.62.

Electrospray Mass Spectrum: M+1 = 302.

Example 14

Preparation of N-2-(4-(3-thienyl)phenyl)propyl acetamide.



A. Preparation of N-2-(4-(3-thienyl)phenyl)-N-*t*-butoxycarbonylpropyl amine: To a degassed solution of 8.2 g (26.0 mmol) of material from Preparation 4, 4.0 g (31.2 mmol) of thiophene-3-boronic acid and 5.3 g (39.0 mmol) of potassium carbonate in 75 mL of dioxane and 25 mL of water was added 1.5 g (1.3 mmol) of tetrakis (triphenylphosphine)palladium(0). The mixture was heated at 90 °C for 18 hr. The mixture was cooled to ambient temperature and 200 mL of water and 100 mL of ether was added. The organic layer was separated and the aqueous layer was extracted three times with 60 mL each of ether. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (500 g of silica gel, 10% ethyl acetate/hexanes) of the residue afforded 7.8 g (94%) of N-2-(4-(3-thienyl)phenyl)-N-*t*-butoxycarbonylpropyl amine.

B. Preparation of 2-(4-(3-thienyl)phenyl)propylamine: A solution of 2.3 g (7.2 mmol) of material from part A in 20 mL of dichloromethane and 5 mL of trifluoroacetic acid was stirred at room temperature for three hours. The mixture

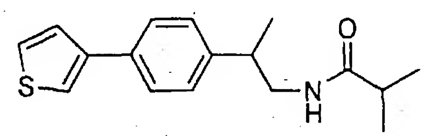
was concentrated *in vacuo* and the residue was dissolved in 20 mL of ethyl acetate. This solution was washed once with saturated aqueous sodium bicarbonate. The organic portion was separated and the aqueous portion was extracted four times with 10 mL each of ethyl acetate. The combined organics were dried anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford 1.5 g (100%) of 2-(4-(3-thienyl)phenyl)propylamine.

C. To a solution of 1.0 mL (0.088 mmol) of a 0.088 M solution of 2-(4-(3-thienyl)phenyl)propylamine in tetrahydrofuran was added 37 mg (0.132 mmol) of piperidinylmethyl polystyrene. To the mixture was added 10.4 mg (0.132 mmol) of acetyl chloride and the mixture was shaken for 6 hours. To this mixture was added 0.15 g (0.3 mmol) of aminomethyl polystyrene and the vessel was shaken for 12 hours. The reaction mixture was filtered through a cotton plug and concentrated to afford the title compound. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 260.

Example 15

Preparation of N-2-(4-(3-thienyl)phenyl)propyl 2-methylpropionamide.

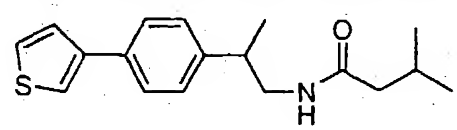


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and isobutyryl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 288.

Example 16

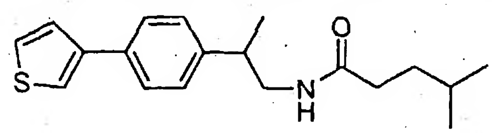
Preparation of N-2-(4-(3-thienyl)phenyl)propyl 3-methylbutyramide.



The title compound from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and isovaleryl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure. Electrospray Mass Spectrum : M+1 = 302.

Example 17

Preparation of N-2-(4-(3-thienyl)phenyl)propyl 4-methylvaleramide.

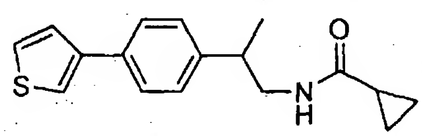


The title compound was prepared 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and isovaleryl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 316.

Example 18

Preparation of N-2-(4-(3-thienyl)phenyl)propyl cyclopropylamide.

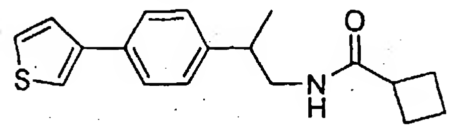


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and cyclopropanecarbonyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 286.

Example 19

Preparation of N-2-(4-(3-thienyl)phenyl)propyl cyclobutylamide.

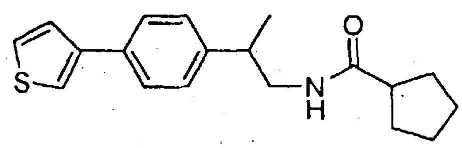


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and cyclobutanecarbonyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 300.

Example 20

Preparation of N-2-(4-(3-thienyl)phenyl)propyl cyclopentylamide.

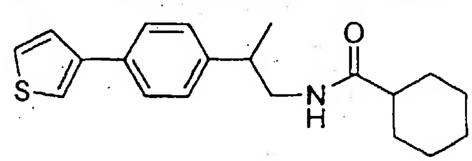


The title compound was prepared 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and cyclopentanecarbonyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 314.

Example 21

Preparation of N-2-(4-(3-thienyl)phenyl)propyl cyclohexylamide.



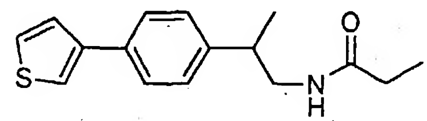
The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and cyclohexanecarbonyl chloride in a manner analogous to

the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 328.

Example 22

Preparation of N-2-(4-(3-thienyl)phenyl)propyl propionamide.

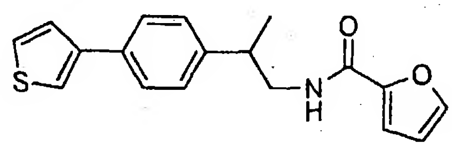


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and propionyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 274.

Example 23

Preparation of N-2-(4-(3-thienyl)phenyl)propyl 2-furylamide.

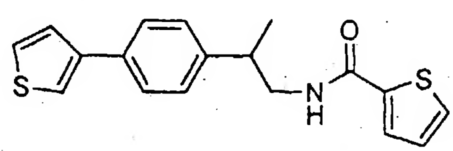


The title compound was prepared 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and 2-furoyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 312.

Example 24

Preparation of N-2-(4-(3-thienyl)phenyl)propyl 2-thienylamide.

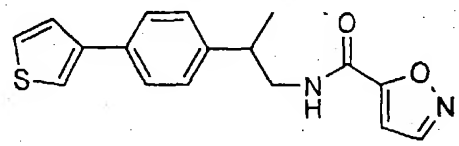


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and 2-thiophenecarbonyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 328.

Example 25

Preparation of N-2-(4-(3-thienyl)phenyl)propyl 5-oxazoylamide.

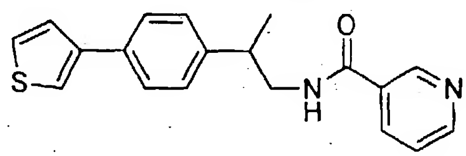


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and oxazole-5-carbonyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 313.

Example 26

Preparation of N-2-(4-(3-thienyl)phenyl)propyl nicotinamide.

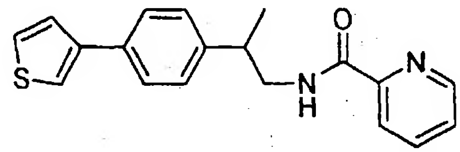


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and nicotinoyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 323.

Example 27

Preparation of N-2-(4-(3-thienyl)phenyl)propyl picolinamide.

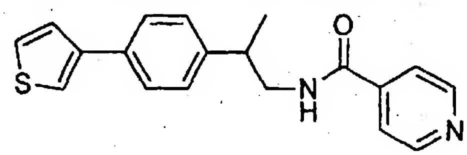


The title compound was prepared 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and picolinoyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 323.

Example 28

Preparation of N-2-(4-(3-thienyl)phenyl)propyl isonicotinamide.

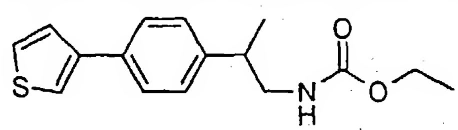


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and isonicotinoyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 323.

Example 29

Preparation of N-2-(4-(3-thienyl)phenyl)propyl ethylcarbamate.

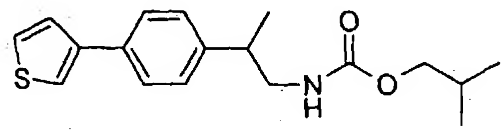


The title compound was prepared 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and ethyl chloroformate in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 290.

Example 30

Preparation of N-2-(4-(3-thienyl)phenyl)propyl 2-methylpropylcarbamate.

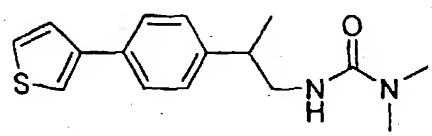


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and 2-methylpropyl chloroformate in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 318.

Example 31

Preparation of N,N-dimethyl-N'-2-(4-(3-thienyl)phenyl)propyl urea.

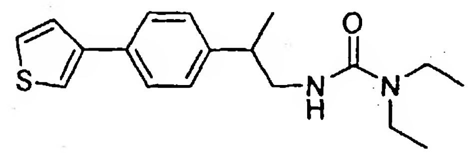


The title compound was prepared 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and N,N-dimethylcarbamoyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 289.

Example 32

Preparation of N,N-diethyl-N'-2-(4-(3-thienyl)phenyl)propyl urea.

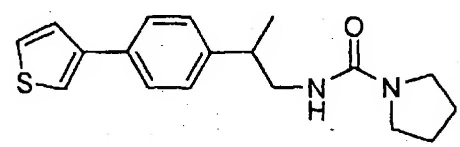


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and N,N-diethylcarbamoyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 317.

Example 33

Preparation of N-2-(4-(3-thienyl)phenyl)propyl-1-pyrrolidinecarboxamide.

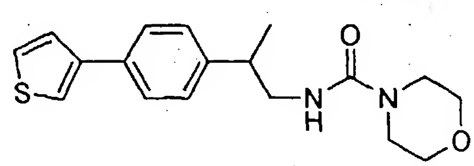


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and pyrrolidine carbonyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.

Electrospray Mass Spectrum : M+1 = 315.

Example 34

Preparation of N-2-(4-(3-thienyl)phenyl)propyl-4-morpholinecarboxamide.

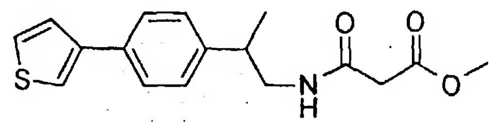


The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and 4-morpholine carbonyl chloride in a manner analogous to

the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.
Electrospray Mass Spectrum : M+1 = 331.

Example 35

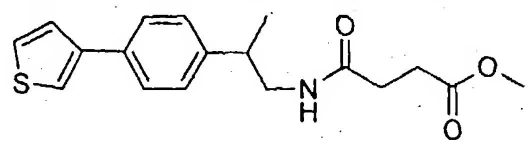
Preparation of N-2-(4-(3-thienyl)phenyl)propyl methyl malonamide



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and methyl malonyl chloride in a manner analogous to the procedure described in example 14. THE NMR SPECTRUM was consistent with the proposed title structure.
Electrospray Mass Spectrum : M+1 = 318.

Example 36

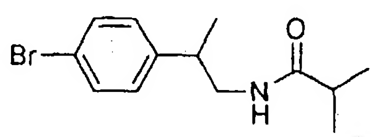
Preparation of N-2-(4-(3-thienyl)phenyl)propyl methyl succinamide



The title compound was prepared from 2-(4-(3-thienyl)phenyl)propylamine (see example 14) and methyl succinyl chloride in a manner analogous to the procedure described in example 14. The NMR spectrum was consistent with the proposed title structure.
Electrospray Mass Spectrum : M+1 = 332.

Example 37

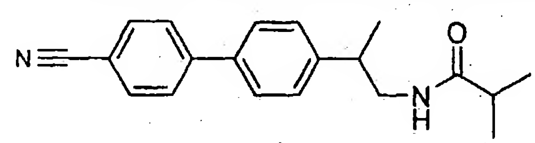
Preparation of N-2-(4-bromophenyl)propyl-2-propanamide.



2-(4-bromophenyl)propylamine (5.0 g, 19.98 mmol) was suspended in dry CH_2Cl_2 (150 mL) and triethylamine (6.1 mL, 43.96 mmol) was added dropwise via addition funnel. The reaction was stirred at room temperature under N_2 for 15 min. and then isobutyryl chloride (2.3 mL, 23.98 mmol) was added dropwise. The reaction was stirred at room temperature overnight. 150 mL of a 1 M sol. of HCl was added. The organic layer was separated and washed with saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered and concentrated to give 5.2 g (91%) of title compound as a white crystalline solid that was sufficiently pure to be used without further purification.

Example 38

Preparation of N-2-[4-(4-cyanophenyl)phenyl]propyl-2-propanamide.



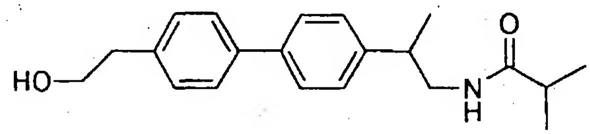
N-2-(4-bromophenyl)propyl-2-propanamide (1.0 g, 3.52 mmol) was combined with potassium acetate (1.04 g, 10.56 mmol) and bis(pinacolato)diboron (0.98 g, 3.87 mmol) in a three-neck round bottom flash under an atmosphere of N_2. Bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.087 g, 0.11 mmol) was added followed by 20 mL of anhydrous DMF and the reaction was heated at 80°C for 3 hours then cooled to room temperature. 4-bromophenyl nitrile (1.3 g, 7.04 mmol) was added followed by additional $PdCl_2$(dppf) (0.087 g, 0.11 mmol). 8.8 mL of a 2M solution of Na_2CO_3 (17.60 mmol) was added and the reaction was heated at 80°C overnight. After cooling to room temperature 1 M HCl solution was added and the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and concentrated to a brown oil. The crude material was purified by chromatography (30% ethyl acetate/70% hexanes to give 0.58 g (54%) of the title compound as a white crystalline solid.

LRMS(ES^+): 307.2 (M+1)

Anal. Calc'd for $C_{20}H_{22}N_2O$+0.25 H_2O: C 77.26, H 7.29, N 9.01; Found C 77.84, H 7.24, N 8.92.

Example 39

Preparation of N-2-[4-(4-(2-hydroxy)ethylphenyl)phenyl]propyl-2-propanamide.



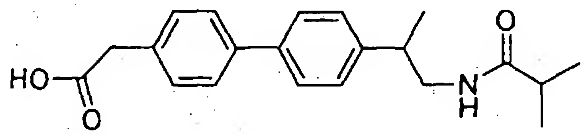
N-2-(4-bromophenyl)propyl-2-propanamide (2.0 g, 7.04 mmol) was combined with potassium acetate (5.4 g, 21.12 mmol) and bis(pinacolato)diboron (0.98 g, 3.87 mmol) in a three-neck round bottom flash under an atmosphere of N_2. Bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.172 g, 0.21 mmol) was added followed by 50 mL of anhydrous DMF and the reaction was heated at 80°C for 3 hours then cooled to room temperature. 4-bromophenyl ethanol (2.8 g, 14.08 mmol) was added followed by additional $PdCl_2$(dppf) (0.172 g, 0.21 mmol). 17.6 mL of a 2M solution of Na_2CO_3 (35.20 mmol) was added and the reaction was heated at 80°C overnight. After cooling to room temperature the reaction mixture was filtered through Celite. The filtrate was diluted with ethyl acetate and washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to a brown oil. The crude material was purified by chromatography (1:1 (v/v) ethyl acetate/hexanes to give 1.80 g (80%) of the title compound as a light yellow solid.

LRMS(ES^+): 326.4 (M+1)

Anal. Calc'd for $C_{20}H_{22}N_2O$+0.5 H_2O: C 75.41, H 8.44, N 3.96; Found C 75.14, H 8.41, N 4.19.

Example 40

Preparation of N-2-[4-(4-carboxymethylphenyl)phenyl]propyl-2-propanamide.

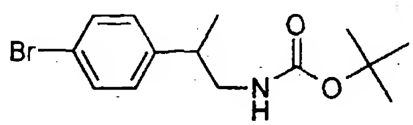


The title compound prepared above in example 39 (0.10 g, 0.31 mmol) was dissolved in anhydrous N,N-dimethylformamide (10 mL) and pyridinium dichromate (PDC, 1.2 g, 3.1 mmol) was added in small portions. The reaction was stirred at room temperature for 24 hours then partitioned between methylene chloride and 1 M HCl. The organic layer was separated and extracted with saturated $NaHCO_3$. The aqueous layer was separated and acidified to pH 2 with 1 M HCl and extracted with methylene chloride. The organic layer was dried ($MgSO_4$), filtered and concentrated to a yellow solid which was recrystallized from cyclohexane/methylene chloride to provide the title compound as a fine white solid.

LRMS(FD$^+$): 339 (M$^+$)

Example 41

Preparation of N-2-(4-bromophenyl)propyl-N-tert-butyl carbamate.

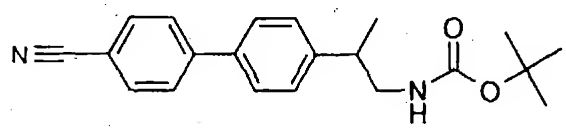


2-(4-bromophenyl)propylamine (6.0 g, 23.98 mmol) was suspended in dry CH_2Cl_2 (80 mL) and triethylamine (8.4 mL, 59.95 mmol) was added dropwise via addition funnel. The reaction was cooled to 0°C and stirred.under N_2 for 15 min. and then di-tert-butyl dicarbonate (5.8 mL, 26.38 mmol) was added in a single portion. The reaction was stirred at room temperature overnight. 50 mL of a 1 M sol. of HCl was added and the reaction mixture was extracted with diethyl ether. The organic layer was separated and washed with saturated $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to give 7.0 g (93%) of the title compound as a white crystalline solid that was sufficiently pure to be used without further purification.

Anal. Calc'd for $C_{14}H_{20}NO_2Br$: C 53.51, H 6.42, N 4.46; Found C 53.27, H 6.34, N 4.37.

Example 42

Preparation of N-2-(4-(4-cyanophenyl)phenyl)propyl-N-tert-butyl carbamate.

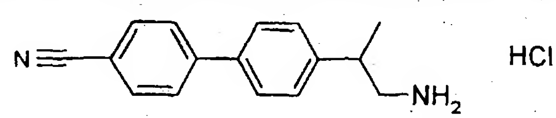


N-2-(4-bromophenyl)propyl-N-tert-butyl carbamate (2.5 g, 7.96 mmol) was combined with 4-cyanophenylboronic acid (1.4 g, 9.55 mmol) and $Pd(PPh_3)_4$ (0.37 g, 0.32 mmol) in dry 1,4-dioxane (40 mL) under N_2 at room temperature. 12 mL of a 2 M solution of Na_2CO_3 were added and the reaction was heated at 60°C overnight then cooled to room temperature and poured into diethyl ether. The mixture was extracted with 1 M HCl, saturated $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to a yellow oil that was purified by chromatography (20% ethyl acetate/80% hexanes) to give 2.4 g (89%) of title compound as a light yellow solid.

Anal. Calc'd for $C_{21}H_{24}N_2O_2$+0.5 H_2O: C 73.01, H 7.30, N 8.11; Found C 73.11, H 7.10, N 8.06.

Example 43

Preparation of N-2-(4-(4-cyanophenyl)phenyl)propylamine HCl.



The title compound prepared above in Example 42 (2.0 g, 5.95 mmol) was combined with anisole (0.064 mL, 0.59 mmol) in dry CH_2Cl_2 (30 mL) while stirring under N_2. Trifluoroacetic acid (4.6 mL, 59.50 mmol) was added dropwise and the reaction was stirred at room temperature overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate and 4 M NaOH. The organic layer was separated and dried ($MgSO_4$), filtered, and concentrated to a

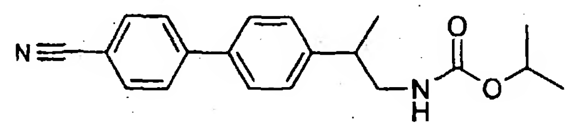
yellow oil. The oil was dissolved in diethyl ether and HCL gas was bubbled through the solution until a white precipitate formed. The precipitate was collected by filtration and washed with diethyl ether. 1.1 g (69%) of the title compound were isolated.

LRMS (ES^+): 237.0 (M+1)

LRMS (ES^-): 236.2 (M-1)

Example 44

Preparation of N-2-(4-(4-cyanophenyl)phenyl)propyl-N-isopropyl carbamate.



The title compound prepared in Example 43 was suspended in dry CH_2Cl_2 (2.0 mL) and triethylamine (0.13 mL, 0.93 mmol) was added followed by the addition of isopropyl chloroformate (0.56 mL, 0.56 mmol). The reaction was stirred at room temperature overnight. The solvent was evaporated and the crude residue was purified by chromatography (30% ethyl acetate/70% hexanes) to give 101 mg (85%) of the title compound.

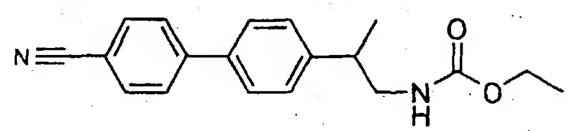
LRMS (ES^+): 323.4 (M+1)

LRMS (ES^-): 381.3 (M+59)

Anal. Calc'd for $C_{20}H_{22}N_2O_2$+0.5 H_2O: C 72.48, H 6.99, N 8.45; Found C 72.71, H 6.67, N 8.27.

Example 45

Preparation of N-2-(4-(4-cyanophenyl)phenyl)propyl-N-ethyl carbamate.



The title compound was prepared as described in Example 44 from the product of Example 43 and ethyl chloroformate. Chromatography (20% ethyl acetate/ 80% hexanes) gave the title compound in 87% yield.

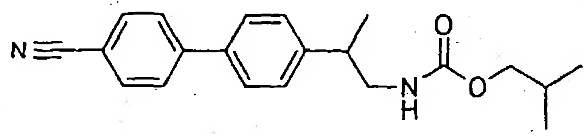
LRMS (ES^+): 309.2 (M+1)

LRMS (ES$^-$): 367.1 (M+59)

Anal. Calc'd for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; Found C 73.86, H 6.54, N 8.92.

Example 46

Preparation of N-2-(4-(4-cyanophenyl)phenyl)propyl-N-isobutyl carbamate.



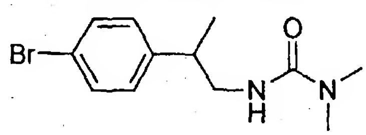
The title compound was prepared as described in Example 44 from the product of Example 43 and isobutyl chloroformate. Chromatography (30% ethyl acetate/ 70% hexanes) gave the title compound in 87% yield.

LRMS (ES$^+$): 337.3 (M+1)

LRMS (ES$^-$): 395.1 (M+59)

Example 47

Preparation of N-2-(4-bromophenyl)propyl-N,N-dimethylurea.

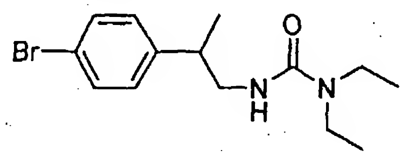


2-(4-bromophenyl)propylamine (5.0 g, 19.95 mmol) was suspended in dry CH_2Cl_2 (100 mL) and triethylamine (6.1 mL, 43.89 mmol) was added dropwise via addition funnel. The reaction was stirred at room temperature under N_2 for 15 min. and then N,N-dimethylcarbamoyl chloride (2.2 mL, 23.94 mmol) was added dropwise. The reaction was stirred at room temperature overnight. 100 mL of a 1 M sol. of HCl was added and the reaction mixture was extracted with diethyl ether. The organic layer was separated and washed with saturated $NaHCO_3$, H_2O, saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to give a white solid that recrystallized from diethyl ether/hexanes to give 5.2 g (91%) of the title compound as a white crystalline solid.

Anal. Calc'd for $C_{12}H_{17}N_2OBr$: C 50.54, H 6.01, N 9.82; Found C 50.83, H 6.06, N 9.65.

Example 48

Preparation of N-2-(4-bromophenyl)propyl-N,N-diethylurea.

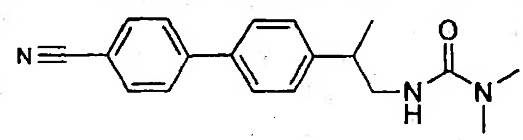


The title compound was prepared from 2-(4-bromophenyl)propylamine and N,N-diethylcarbamoyl chloride as described in Example 47. 2.4 g (96%) of the title compound was isolated as a clear oil.

LRMS (ES^+): 312.9, 314 (M+2)

Example 49

Preparation of N-2-(4-(4-cyanophenyl)phenyl)propyl-N,N-dimethyl urea.



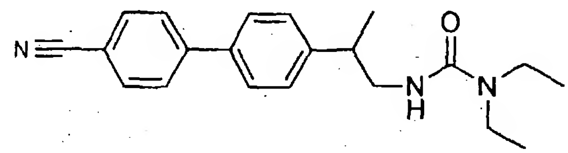
The title compound prepared in Example 47 (1.0 g, 3.51 mmol) was combined with 4-cyanophenylboronic acid (0.62 g, 4.21 mmol) and $Pd(PPh_3)_4$ (0.16 g, 0.14 mmol) in dry 1,4-dioxane under N_2 at room temperature. 6 mL of a 2 M solution of Na_2CO_3 were added and the reaction was heated at 60°C for 8 h. then cooled to room temperature and poured into diethyl ether. The mixture was extracted with H_2O and saturated NaCl, dried ($MgSO_4$, filtered, and concentrated to a brown oil that was purified by chromatography (1:1 (v/v) ethyl acetate/hexanes) to give 0.63 g (58%) of a tan solid.

LRMS (ES^+): 308.0 (M+1)

LRMS (ES^-): 366.0 (M+59)

Example 50

Preparation of N-2-(4-(4-cyanophenyl)phenyl)propyl-N,N-diethyl urea.



The title compound was prepared in a manner analogous to that described in Example 49 from the reaction of N-2-(4-bromophenyl)propyl-N,N-diethylurea prepared in Example 48 and 4-cyanophenylboronic acid.

LRMS (ES^+): 336.0 (M+1)

Example 51

Preparation of intermediate N-2-(4-bromophenyl)ethyl methanesulfonamide.

To a 0°C solution of of 4-bromophenethylamine (10.0 g, 50.0 mmol) and triethylamine(7.7 mL, 55.0 mmol) in 150 mL of dichloromethane was added dropwise methanesulfonyl chloride(4.3 mL 55.0 mmol) in 20 mL of dichloromethane. After two hours, the reaction mixture was washed once with 100 mL of 10% aqueous sodium bisulfate. The organic portion was separated and the aqueous portion was extracted three times with 50 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 14.0 g (100%) of the intermediate title compound.

Preparation of intermediate N-2-(4-tri-n-butylstannylphenyl)ethyl methanesulfonamide.

The intermediate title compound (10.0 g) was prepared in a manner analogous to Preparation 40 described in International Patent Application Publication WO 98/33496 published August 6, 1998, which is incorporated herein by reference, starting from N-2-(4-bromophenyl)ethyl methanesulfonamide, prepared directly above.

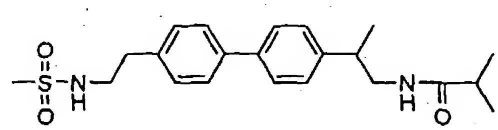
Preparation of intermediate N-t-butoxycarbonyl-N-(2-(4-phenyl)propyl-2-methanesulfonamide.

To a solution of 3.2 g (10.2 mmol) of 2-(4-bromophenyl)-N-(*t*-butoxycarbonyl)propylamine (See Preparation 4 above) and N-2-(4-tri-n-butylstannylphenyl)ethyl methanesulfonamide (5.0 g, 10.2 mmol)in 30 mL of toluene was added palladium acetate(0.11 g (0.51 mmol) and triphenylphosphine (0.27 g,1.02 mmol). The mixture was heated to 100°C for 16 hours, cooled to room temperature and diluted with 30 mL of ethyl acetate. The mixture was filtered through celite and concentrated *in vacuo*. Chromatography (250 g of silica gel, 20% ethyl acetate/hexanes) afforded 1.7 g (39%) of the intermediate title compound.

Preparation of intermediate N-(2-(4-Phenyl)propyl-2-methanesulfonamide.

To a solution of of N-t-butoxycarbonyl-N-(2-(4-phenyl)propyl-2-methanesulfonamide (1.7 g, 3.9 mmol in 16 mL of dichloromethane was added 4 mL of trifluoroacetic acid. The reaction mixture was stirred at room temperature for two hours and concentrated *in vacuo*. The residue was dissolved in 20 mL of dichloromethane and washed one time with 15 mL of 1 N sodium hydroxide. The organic portion was separated and the aqueous portion was extracted three times with 10 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 1.3 g (97%) of the intermediate title compound.

Preparation of N-2-(4-(4-(2-methanesulfonamidoethyl)phenyl)phenyl)propyl 2-methylpropionamide.

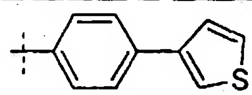
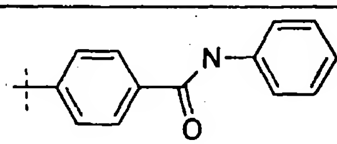
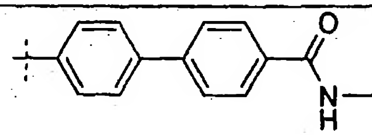
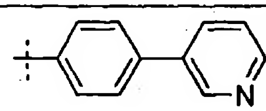
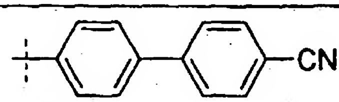
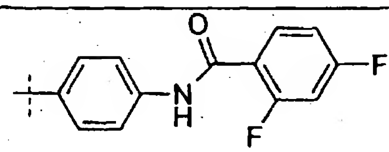
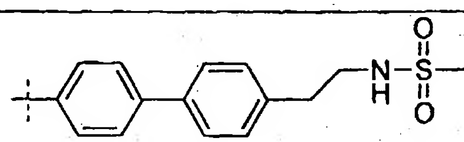
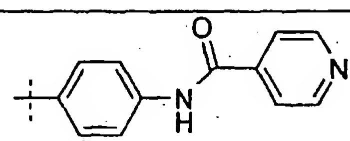
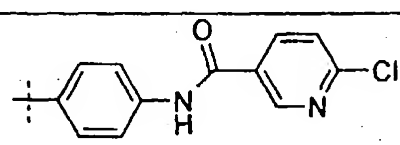


To a room temperature solution of N-(2-(4-Phenyl)propyl-2-methanesulfonamide (0.15 g, 0.45 mmol) and triethylamine (0.06mL, 0.45 mmol) in 2 mL of dichloromethane was added dropwise isobutyryl chloride(47uL,.45 mmol) and the reaction mixture was stirred for 16 hours. The reaction mixture

was washed once with 2 mL of 10% aqueous sodium bisulfate. The organic portion was separated and the aqueous portion was extracted three times with 2 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was recrystallized from chlorobutane/ethyl acetate, filtered and dried in vacuo at 60°C to afford 0.04 g (22%) of the title compound.

Mass Spectrum: M+1 = 403.

The following Table I specifically illustrates additional preferred substituents for R^1 Table I.

$\underline{R^1}$










The following Table II illustrates additional preferred compounds of the present invention wherein R^{30} and R^{31} are defined as hereinabove for formulas I' and I". The following compounds can be prepared by one of ordinary skill in the art in a manner analogous to the techniques and procedures described hereinabove.

Table II.